WAUSAU PHARMACY BENEFITS

WAUSAU

Dollars & Sense

Your Rx for Better Health

April 2000, Vol. 2, No. 1

Welcome to Dollars & Sense, Your Rx for Better Health – a newsletter for Wausau Pharmacy Benefits (WPB) members. To assist employers and their enrollees with the rising cost of prescription drugs, WPB developed this newsletter. Dollars & Sense will be published quarterly and focus on a variety of issues that can assist enrollees in lowering these costs while maintaining the highest level of benefit.

The rising cost of prescription drugs

Consider these facts:

- 2.97 billion prescriptions were dispensed in 1999, up from 2.73 in 1998
- The cost of these prescriptions is an estimated $121.6 billion in 1999, up from $103.5 billion in 1998
- Experts suggest that this trend is not expected to change and consumers will purchase a staggering four billion prescriptions by 2005

The anticipated increases are based on factors such as direct to consumer advertising, the aging of the American population, and the advent of many new therapies in recent years for the management of chronic illnesses. With predictions like this, its no wonder people are talking about the increasing cost of prescription drugs.

Waste vs. benefit

Is more better or is more simply more?

There is little doubt that there is a significant amount of waste in the form of prescription benefits today. The waste associated with medications usually take the form of overutilization or the use of higher cost medications over equivalent lower cost therapies.

Medications do offer us many advantages and it should not be overlooked that they can have a positive effect on our ability to prevent certain diseases, improve our quality of life, and decrease health care costs in other areas.

For employers that sponsor health benefits, particularly prescription benefits, this means continued increases in prescription related expenses. This translates into higher premiums for health insurance as well as higher out-of-pocket expenses for members.

To split or not to split

In *Dollars & Sense*, we will look at the subject of splitting tablets as a way to lower prescription costs.

Pill splitting is not a new concept. For many people who do not have a prescription benefit, it has been an effective way to help them lower their prescription costs. However, in recent years, this has become a controversial topic as some managed care organizations have implemented programs requiring patients to use half tablets of certain medications.

In assessing whether or not pill splitting is or is not a good idea, the potential benefits and concerns associated with this practice need to be examined.

Benefits of pill splitting

The compelling benefit to cutting a single tablet into two pieces is strictly financial. Many medications are parity priced (i.e. various strengths of the same medication cost the same amount per tablet). When this is the case, cutting a tablet in half is simply cutting its cost in half for the party paying the cost. When the payor is an individual without insurance the benefit is clear. But what about someone that has prescription coverage through their employer? For this individual the benefit of splitting a tablet is twofold:

(1) A 30-day supply of medication can be changed into a 60-day supply. This may mean fewer copayments and lower out-of-pocket expense for the member.

(2) The member has reduced costs for their employer which can ultimately help to keep premium costs down.

Example:

Consider the difference in cost to a member and their plan under the following circumstances. Zoloft 50mg a day, coinsurance of 20 percent per 30-day supply.

Drug	Qty	Day Supply	Cost to Plan	Cost to Member
Zoloft 50mg 1 tab/day	30	30	$54.32	$10.86
Zoloft 100mg ½ tab/day	30	60	$60.47	$12.09

Concerns with pill splitting

Pill splitting is only appropriate for certain medications such as medications intended only for a short duration (pain medications) or medications that stay in the blood stream for a long period of time. An example of a long acting medication would be antidepressants, specifically those known as Selective Seratonin Reuptake Inhibitors (SSRI's)—Paxil, Celexa, Zoloft (Prozac is not included as it is manufactured in capsule form and not as a tablet). While it is desirable that a person take an identical dose of these medications every day, variations in dose of 5-10 percent are not likely to produce any clinical relevance.

Some medications are scored and are therefore better candidates for pill splitting. It should be noted that certain medications for chronic diseases should never be considered for pill splitting, such as some sustained released medications (i.e. Procardia XL, Adalat CC), medications with a narrow therapetic window (Coumadin, Lanoxin), or medications with enteric coating.

Included with this article is a list of medications that may be appropriate for splitting. The medications on this list are either parity priced or have minimal price difference for various strengths. This list is not to be considered a complete listing of all medications in tablet form that might be suitable for splitting. If you are currently taking one of these medications and would like to consider pill splitting, we recommend that you:

1. **Consult with your physician.** If your physician agrees that this is an appropriate way for you to lower your cost, have them clearly write a prescription for the higher dosage of medication with directions to be taken as one-half tablet. If your physician does not feel that this is an appropriate opportunity to lower your prescription costs, ask them if there are other alternatives to lower your prescription expenses.

2. **Purchase a pill splitting device from a local pharmacy.** These devices are relatively inexpensive (around $2-$3) and will enable you to cut tablets more accurately and safely.

3. **Take your medication as directed.** Despite the many advances made with medications in recent years, compliance continues to be one of the most costly factors that contribute to the rising cost of health care. The most costly medication is the medication that sits in the bottle and is never used for its intended purpose. If you have any questions about the medications that you are taking such as side effects or the inconvenience of having to take multiple doses of medication per day, talk with your physician or pharmacist. Chances are that there is a similar medication that you can take that may not cause the same side effects or is more convenient to take.

Medications that may be appropriate for pill splitting

Drug	Average Wholesale Price	Comments
Atorvastatin (Lipitor)		Oval, film-coated tablets
10mg #90	$154.15	
20mg #90	$253.80	
40mg #90	$305.65	
Alendronate (Fosamax)		Round uncoated, unscored tablets.
5mg #30	$59.12	Manufacturer recommends against tablet splitting
10mg #30	$59.12	due to potential pulmonary irritation.
Benazepril (Lotensin)		Round tablets
5mg #100	$83.38	
10mg #100	$83.38	
20mg #100	$83.38	
40mg #100	$83.38	
Candesartan (Atacand)		Round tablets
4mg #30	$36.00	
8mg #30	$36.00	
16mg #30	$36.00	
32mg #30	$50.40	

Drug	Average Wholesale Price	Comments
Carvediol (Coreg)		Oval, film-coated tablets. Tiltab shape of 6.25, 12.5, and 25mg tablets makes them difficult to cut. Accuracy of dose may be especially important for patients with heart failure.
3.125mg #100	$154.50	
6.25mg #100	$154.50	
12.5mg #100	$154.50	
25mg #100	$154.50	
Cetirizine (Zyrtec)		Rectangular, film-coated, unscored tablets
5mg #100	$185.99	
10mg #100	$185.99	
Cilstazol (Pletal)		
5mg #60	$89.25	Triangular tablets
10mg #60	$89.25	Round tablets
Citalopram (Celexa)		Oval, scored, film-coated tablets
20mg, #100	$201.70	
40mg #100	$210.47	
Donepezil (Aricept)		Round, film-coated, unscored
5mg #30	$126.45	
10mg #30	$126.45	
Doxazosin (Cardura)		Oval, scored tablets
1mg #100	$99.63	
2mg #100	$99.63	
4mg #100	$104.58	
8mg #100	$104.58	
Fluvoxamine (Luvox)		
25mg #100	$225.89	Unscored, elliptical, film-coated tablets
50mg #100	$252.41	Scored, elliptical, film-coated tablets
100mg #100	$258.90	Scored, elliptical, film-coated tablets
Fosinipril (Monopril)		
10mg #30	$26.91	Diamond shaped, partially scored tablets
20mg #30	$26.91	Oval tablets
40mg #30	$26.91	Hexagonal tablets
Irbesartan (Avapro)		Oval tablets with curved sides
75mg #30	$35.72	
150mg #30	$37.60	
300mg #30	$45.19	
Leflunomide (Arava)		
10mg #30	$244.80	Round, film-coated tablets
20mg #30	$244.80	Triangular, film-coated tablets
Lisinopril (Prinivil)		
2.5mg #100	$58.08	Round tablets
5mg #100	$87.01	Shield-shaped, scored tablets
10mg #100	$89.92	Shield-shaped tablets
20mg #100	$96.24	Shield-shaped tablets
40mg #100	$140.66	Shield-shaped tablets

Drug	Average Wholesale Price	Comments
Losartan (Cozaar)		Teardrop-shaped, film-coated tablets
25mg #100	$125.10	
50mg #100	$125.10	
100mg #100	$187.50	
Mirtazapine (Remeron)		
15mg #30	$69.72	Oval, scored tablets
30mg, #30	$71.83	Oval, scored tablets
45mg #30	$76.50	Oval, tablets
Moexipril (Uniivasc)		Round, film-coated tablets
7.5mg #100	$59.18	
15mg #100	$59.18	
Nefazodone (Serzone)		
50mg #60	$69.32	Hexagonal tablets
100mg #60	$69.32	Hexagonal, scored tablets
150mg #60	$69.32	Hexagonal, scored tablets
200mg #60	$69.32	Hexagonal tablets
250mg #60	$69.32	Hexagonal tablets
Paroxetine (Paxil)		
10mg #30	$66.95	Film-coated, oval tablets
20mg #30	$69.85	Film-coated, scored oval tablets
30mg #30	$71.95	Film-coated, oval tablets
40mg #30	$76.00	Film-coated, oval tablets
Perindopril (Aceon)		Oblong tablets, scored on one side
2mg #100	$98.00	
4mg #100	$98.00	
8mg #100	$140.00	
Quinapril (Accupril)		
5mg #90	$88.06	Elliptical, film-coated scored tablets
10mg #90	$88.06	Triangular, film-coated tablets
20mg #90	$88.06	Round, film-coated tablets
40mg #90	$88.06	Elliptical, film-coated tablets
Rizatriptan (Maxalt)		
5mg #6	$84.07	Round, shallow-cup tablets
10mg #6	$84.07	Round tablets
Ropinirole (Requip)		Pentagonal Tiltab film-coated tablets with beveled edges
0.25mg #100	$97.30	
0.5mg #100	$97.30	
1mg #100	$97.30	
2mg #100	$97.30	
5mg #100	$194.60	
Sertraline (Zoloft)		Capsule-shaped, film-coated, scored tablets
25mg #50	$109.98	
50mg #100	$227.14	
100mg #100	$233.70	

Drug	Average Wholesale Price	Comments
Sildenafil (Viagra)		Diamond-shaped, film-coated tablets
25mg #30	$262.50	
50mg #30	$262.50	
100mg #30	$262.50	
Simvastatin (Zocor)		
5mg #60	$106.84	Shield-shaped, film-coated tablets
10mg #60	$130.89	Shield-shaped, film-coated tablets
20mg #60	$228.33	Shield-shaped, film-coated tablets
40mg #60	$228.33	Shield-shaped, film-coated tablets
80mg #60	$228.33	Capsule-shaped, film-coated tablets
Tolterodine (Detrol)		Round, film-coated tablets with curved sides
1mg #60	$75.60	
2mg #60	$77.58	
Trandolapril (Mavik)		
1mg #100	$68.42	Round, scored tablets
2mg #100	$68.42	Round tablets
4mg #100	$68.42	Round tablets
Venlafaxine (Effexor)		Shield-shaped (5-sided), scored tablets
25mg #100	$112.83	
37.5mg #100	$116.20	
50mg #100	$119.66	
75mg #100	$126.88	
100mg #100	$134.48	
Zalcitabine (Hivid)		Oval, film-coated tablets
0.375mg #100	$193.67	
0.75mg #100	$242.75	

We would like to thank you for taking the time to read this edition of *Dollars & Sense, Your Rx for Better Health.* If you have comments that you would like to share with us about this edition or suggestions for future editions, please contact us at www.wausau.com or email us at wpb@wausau.com.

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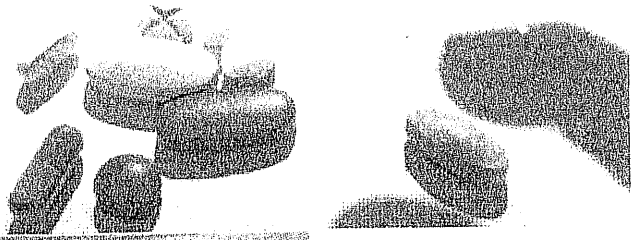
BEST BUY DRUGS™

Free Guidance for Consumers on Prescription Medicines



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- Drugs for Heartburn, Acid Reflux Disease – PPIs
- Schizophrenia, Bipolar Disorder
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- Asthma and Lung Disease – Inhaled Steroids
- Alzheimer's Disease Drugs
- Migraine Headache Drugs – Triptans
- Menopause – Female Hormones
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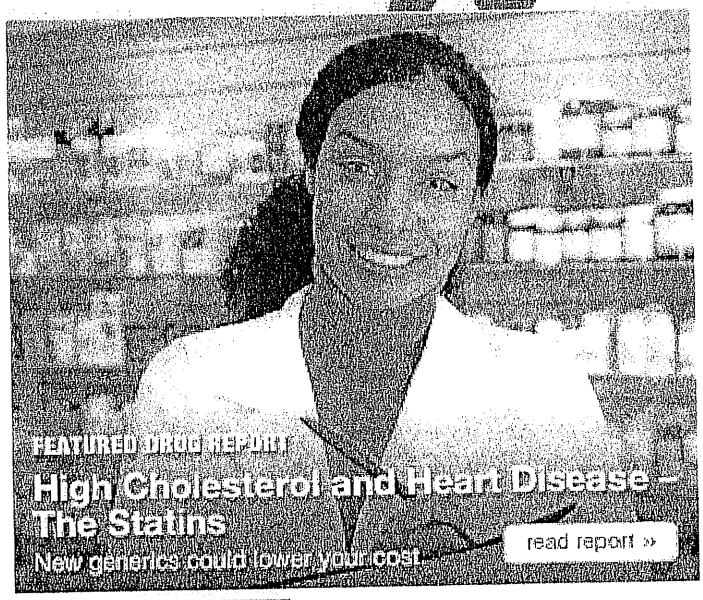
Full List >>



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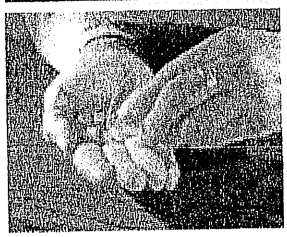

Pill-Splitting

It's safe and can save you lots of money

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SHOPPER'S GUIDE TO PRESCRIPTION DRUGS – NUMBER 1

Pill Splitting

If you take prescription drugs to treat a chronic illness, you could save money by splitting your pills – literally cutting them in half. Not all pills can be split, so pill splitting cannot be used in the treatment of every chronic disease. But in the face of mounting costs for prescription drugs, many doctors and health authorities are advising this strategy with more and more medicines. Most notably, all the cholesterol-lowering drugs known as statins can be split as can many of the drugs used to treat high blood pressure and depression.

Essentially, pill splitting allows you to buy two doses of medicine for the price of one – or get two months' worth of medicine for the price of one month. There is no danger in splitting pills as long as your doctor agrees that it's a good idea for you, you learn how to do it properly, and you split only pills that can be split. Simple pill splitting devices are now widely available.

BACKGROUND

Doctors have long counseled patients to split their pills. Initially, this was not to save money. Instead, it was to enable people to take a dose of medicine not readily available from a pharmacist. That's because drug companies make only a few fixed doses of any given medication. But many doctors prefer to tailor the dose of a medicine to a patient's exact needs, or to lower the risk of side effects. For example, a doctor may want to prescribe less of a drug (say, 10mg) than the lowest dose available (say, 20mg).

A common example of pill splitting these days involves good old aspirin. Health authorities now urge anyone at risk for heart disease to take half an adult aspirin tablet a day. A regular aspirin tablet contains 325mg, but studies show that 160mg or less is just as good at lowering the risk of a heart attack or stroke – and safer. Some companies now make half-dose aspirin tablets and children's aspirin comes in lower doses (generally 81mg). But often the least expensive alternative is to buy a large bottle of generic aspirin and split the pills in half.

Pill-splitting saves money because pharmaceutical companies and pharmacies often charge nearly the same amount for a particular medicine regardless of its dose. For example, a once-a-day drug may cost $100 for a month's supply of both a 100mg dose and a 50mg dose. Thus, if your doctor prescribes the 50mg pill, it'll cost you $100. But if he prescribes the 100mg pill and instructs you to cut it in half, $100 will buy you two months worth of medicine. If you take several medicines, that kind of savings can mount up.

Not surprisingly, many insurance companies are in favor of pill-splitting because it saves them money, too. Your employer may like the idea for the same reason. Some insurance companies now provide you with a list of approved drugs to split. And a few are even requiring pill-splitting by not covering the cost of some lower-dose drugs. This forces people to buy higher-dose pills and split them. The American Medical Association and the American Pharmacists Association oppose this practice. But these organizations acknowledge that many pills can be safely split if done correctly. The Department of Veteran's Affairs allows pill splitting at a number of VA facilities, though it does not formally endorse the practice.

Most drug companies oppose pill-splitting. They say it can be dangerous. But studies to date have not shown any adverse impact on health. In addition, by reducing the cost of prescription medicines, pill splitting could improve

SOME MEDICINES THAT CAN BE SAFELY SPLIT

- Amlodipine (Norvasc)
- Atenolol (Tenormin)
- Atorvastatin (Lipitor)
- Citalopram (Celexa)
- Clonazepam (Klonopin)
- Doxazosin (Cardura)
- Finasteride (Proscar)
- Levothyroxine (Synthroid)
- Lisinopril (Zestril)
- Lovastatin (Mevacor)
- Metformin (Glucophage)
- Metoprolol (Toprol)
- Nefazodone (Serzone)
- Olanzapine (Zyprexa)
- Paraxetine (Paxil)
- Pravastatin (Pravachol)
- Quinapril (Accupril)
- Rosuvastatin (Crestor)
- Sertraline (Zoloft)
- Sildenafil (Viagra)
- Simvastatin (Zocor)
- Tadafil (Cialis)
- Vardenafil (Levitra)

health outcomes by helping people afford the drugs they need and comply with the drug regimens their doctors recommend.

PRACTICAL ADVICE

Consult your doctor about pill splitting. The dose you take of most medicines is very important. If you don't get the right dose, the effect of the drug may be substantially reduced. Your doctor should know which drugs can be split and which cannot. You can consult a pharmacist, too, who may be willing to show you how to split your pills.

Pills are only safely split in half and never into smaller portions, such as into thirds or quarters.

There is no official, complete list of medicines that can be split, and some drugs are dangerous to split. That makes it doubly important to consult a doctor or pharmacist. Generally the following kinds of pills should *not* be split:

- Chemotherapy drugs
- Anti-seizure medicines
- Birth control pills
- Blood thinners (Coumadin, warfarin)
- Capsules of any kind that contain powders or gels
- Pills with a hard outside coating
- Pills designed to release the medication over time in your body
- Pills that are coated to protect your stomach
- Pills that provide drug release throughout the day
- Pills that crumble easily, irritate your mouth, taste bitter, or contain strong dyes that could stain your teeth and your mouth.

Examples of medicines that cannot be split include oxycodone (OxyContin) for pain, omeprazole (Prilosec) for heartburn, and cetirizine (Zyrtec) for allergies.

Some pills may deteriorate when exposed to air and moisture for long periods after being split. Therefore, you should not split your pills in advance. Instead, do it on the day you are taking the first half. Then take the remaining half on the second day.

Don't split your pills with a knife. This can be dangerous and generally is imprecise. That is, it leads to unequal halves too often, studies show. Instead, purchase a pill splitter. They cost from $3 to $10 and are available at most pharmacies and large discount stores. A device for splitting oddly shaped pills may cost more, up to $25. Some insurers will send you a pill splitter for free so check with your health plan.

If you have poor eyesight, or if you have an ailment like arthritis or Parkinson's disease, it might be difficult for you to split your pills. You should talk with your doctor about whether it might be too much of a burden. Likewise, people with memory problems or impaired thinking are not good candidates to split their pills.

The easiest pills to split are relatively flat round ones with a scored center. That's a slightly indented line that runs across the center of the pill. However, not every pill that has a scored center is meant to be split. Again, consult your doctor or pharmacist.

PILL SPLITTING SAVINGS – SOME EXAMPLES

Medicine and Daily Dose	Average Monthly Cost [1]	Potential Monthly Savings if Larger Dose Split in Half [2]	Resulting Average Monthly Cost with Split Pills
Lovastatin (Mevacor) 10mg	$33	$14.50	$18.50
Atorvastatin (Lipitor) 40mg	$124	$62.50	$61.50
Amlodipine (Norvasc) 5mg	$55	$18.50	$36.50
Sertraline (Zoloft) 50mg	$98	$49	$49
Metoprolol (Toprol XL) 200mg	$69	$9.50	$34.50

(1) Prices are nationwide retail averages; information derived by Consumer Reports Best Buy Drugs from data provided by Wolters Kluwer Health. (2) Dose used for calculation is double the dose listed in first column. Price of that dose is not given here.

THE SHOPPER'S GUIDE TO PRESCRIPTION DRUGS SERIES

This series is produced by Consumers Union and *Consumer Reports Best Buy Drugs*, a public information project supported by grants from the Engelberg Foundation and the National Library of Medicine of the National Institutes of Health. The project's free Web site is www.CRBestBuyDrugs.org.

PHARMACOECONOMICS

Tablet Splitting

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Others view tablet splitting as a temporary escape from the larger issue of rising drug prices. "I'm glad that [Dr. Parra's] results were positive ... but it's not a solution, it's a Band-Aid," said Daniel Hussar, PhD, Remington Professor of Pharmacy, Philadelphia College of Pharmacy. "The issue that needs to be addressed full force is prices."

Even as a temporary solution, tablet splitting remain risky and underresearched, according to some. The American Society of Consultant Pharmacists' (ASCP) policy statement on mandatory tablet splitting (available at www.ascp.com/public/pr/policy/tabsplit.shtml) warns of forcing extra medication-handling procedures on patients with physical or mental limitations such as arthritis or parkinsonism. ASCP Director of Policy and Advocacy Tom Clark, RPh, MHS, told *Pharmacy Practice News*, "Tablet splitting has been done clinically for many years, usually in cases where the patient needs a lower dose than is commercially available. But we don't want this to become widespread. Patients must be carefully selected and educated."

Both Dr. Hussar and Mr. Clark brought up practical questions involved in tablet-splitting programs. Considering long-term care facilities, Mr. Clark wondered whether already overextended nursing staff would be responsible for splitting tablets and where half-tablets would be stored. Having the pharmacist precut all tablets in a prescription poses its own problems, he noted. "Once a tablet's coating is breached, air and moisture can affect it. Is a half-tablet going to be stable for 30 days?"

Dr. Hussar raised issues regarding patient–pharmacist communications. "If the physician says one pill and the pharmacist says half a pill, who does the patient follow? What if the pharmacist splits the tablet and the patient thinks it still needs to be split?"

The bottom line on tablet splitting for Dr. Hussar remains the bottom line. "Who's saving the money? Is it the patient? The hospital? Pharmacists will spend more time talking to their patients but pharmacy benefits managers aren't going to agree to higher dispensing fees."

However, Dr. Parra noted a recent study showing that statins were the drug most likely to be discontinued by Medicare recipients because of cost. He added: "Although tablet splitting statins is not the solution for rising drug costs, it surely can have a role."

—*Shayna B. Kravetz, BSc*

'Who's saving the money [via tablet-splitting]? Is it the patient? The hospital? Pharmacists will spend more time talking to their patients but pharmacy benefits managers aren't going to agree to higher dispensing fees.'

—Daniel Hussar, PhD

Tablet Splitting

continued from page 1

Participation in the Florida program was voluntary. Tablet splitting eventually became the default for electronic orders of eligible prescriptions, although prescribers, patients or pharmacists could still opt for whole-tablet regimens. During 1999, 3,787 patients received daily doses of simvastatin at 5, 10, 20 or 40 mg. The patients were divided into two groups depending on whether they agreed to undergo voluntary conversion from whole simvastatin tablets to split tablets. Patients' low-density lipoprotein cholesterol (LDL-C) levels were followed through conversion to tablet splitting or, for patients who still received whole-tablet dosages, for at least 45 days.

With data for 1,098 patients in each group, 76.3% of patients in the tablet-splitting group achieved final LDL-C levels <130 mg/dL, versus 73.6% of those receiving whole tablets (P=0.14). The two groups also showed similar changes in LDL-C levels from baseline, and average final LDL-C values overall; patients in the tablet-splitting group averaged 110.9±29.6 mg/dL and patients who received whole tablets averaged 112.1±32.4 mg/dL (P=0.304). Patients' adherence to each regimen, as tracked by prescription refills, and transaminase levels did not differ significantly between the two groups.

The Pros and Cons

One benefit of tablet splitting is that some patients can save money. In a 2004 pilot program for Nebraska government employees, patients were offered $10 off each refill's copay if they split tablets for their prescriptions of sertraline (Zoloft, Pfizer), citalopram (Celexa, Forest), escitalopram (Lexapro, Forest), and atorvastatin (Lipitor, Pfizer). Participants received a tablet splitter and brochure directly from their health plan. In 2004's first quarter, 113 patients saved $2,360 and the state health plan saved $7,300, after paying administrative costs of $4,500, said Nina Homan, PharmD, Director of Pharmacy Programs, Prime Therapeutics, a pharmacy benefits solutions company based in Eagan, Minn.

see Tablet Splitting, page 18

To Split or Not To Split

The following suggestions for tablet splitting are based on an algorithm developed by the American Pharmacists Association Strategic Directions Committee (*J Am Pharm Assoc* 2004;44:324-325) and interviews with Daniel Hussar, PhD, Remington Professor of Pharmacy, Philadelphia College of Pharmacy, and David Parra, PharmD, Clinical Pharmacist, VA Medical Center, West Palm Beach, Fla.

The Prescription

Medications with narrow therapeutic indexes or unfavorable side-effect profiles are not suitable to tablet splitting. Capsules cannot be split, nor can tablets designed to have a sustained release or given enteric coatings to enable effective passage through the digestive system. Tablets should be able to withstand long-term exposure to air and moisture without degrading in texture or efficacy, especially if the pharmacist will split all tablets in advance.

The Patient

Physical limitations that may impede patients' ability to split tablets include lack of visual acuity or limited manual dexterity because of illnesses such as arthritis or parkinsonism and mental limitations such as Alzheimer's disease.

The Pharmacist

The pharmacist should take the following steps:

- Verify the relationship between the daily dosage prescribed and the dosage in the tablet as formulated;
- Ensure that both patient and prescription are suitable for a tablet-splitting program;
- Verify that the patient has a pill splitter and is educated on its use;
- Clarify with the patient what the prescriber has told him or her about the regimen and ensure that the patient receives a consistent message about how many doses to take each day; and
- Follow-up on delay in getting refills to promote patient adherence and to prevent the patient from mistakenly splitting presplit tablets.

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Subject: SF Chronicle - Today's News - Study finds pill splitting safe

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Subject: Today's News - Study finds pill splitting safe

Today's News

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San Francisco Chronicle
NORTHERN CALIFORNIA'S LARGEST NEWSPAPER

Study finds splitting pills usually is safe

By Ron Winslow
Reprinted from the Wall Street Journal
San Francisco Chronicle
Friday, September 1, 2002

The practice of splitting pills to save money on prescription drugs could lead to significant cost savings without risking the effectiveness of the medicines or the safety of patients, researchers say in a new study.

But doctors, health plans and patients should limit the practice to pills that, for both their price and the way they are made, lend themselves to it.

"You need to make sure it's done accurately, with full discussion between patients and physicians," says Randall Stafford, assistant professor of medicine at Stanford University's Center for Research in Disease Prevention and lead author of the study, which appears in the current issue of the American Journal of Managed Care. That being said, pill-splitting "can provide cost savings without really changing the clinical care that patients are getting," Dr. Stafford says.

Economic benefits of the strategy can be considerable. Kevin Graham, a cardiologist at Minneapolis Heart Institute in Minnesota, says prescribing 40 milligram tablets of the cholesterol-lowering drug Zocor for patients who then take just 20 milligrams a day by breaking the pill in two can save $730 a year.

"These people are often taking not one but three or four or five drugs that each cost from $1 to $4 a day," Dr. Graham says. "If you can get them a deal you become their friend."

But if patients, health insurers and employers see pill-splitting as an antidote to the soaring cost of drugs, the pharmaceutical industry sees otherwise.

Big drug companies have consistently warned that the practice could pose a risk to patients by leading to improper or inconsistent dosing and other problems. Kaiser Permanente, a big health-maintenance organization based in Oakland, Calif., that encourages pill-splitting with selective medicines, is defending itself in a lawsuit filed on behalf of some of its members seeking to end the practice.

Dr. Stafford's study is one of the few to examine the safety question and to set out criteria for determining which pills are best suited to cutting.

Dr. Stafford considered a list of 256 medicines commonly prescribed nationally and particularly at a small health plan in Boston during nine months in the year 2000. He and his co-author, David Radley of the Institute for Health Policy at Massachusetts General Hospital in Boston, winnowed them down to a list 48 medicines that could be split. But only 11 were prescribed often enough in the health plan to be found both clinically appropriate and cost-effective for the splitting strategy.

"It's important to note that it's a minority of medications that fall into this category," Dr. Stafford says. Yet he believes the potential for cost savings is substantial because drugs for high blood pressure and high cholesterol as well as antidepressants -- all widely used medications -- were on the final list.

Those on the list include the cholesterol reducer Lipitor and the impotency remedy Viagra, both marketed by Pfizer Inc.; the antidepressants Paxil from GlaxoSmithKline PLC and Celexa from Forest Laboratories Inc.; and the ACE inhibitor lisinopril, marketed as Prinivil by Merck & Co., and as Zestril by AstraZeneca PLC. (Lisinopril just went off patent and thus wouldn't likely now be a cost-effective candidate for pill-splitting.)

The economic advantage results from the fact that many drug companies charge essentially the same price per tablet regardless of the dose. That's to ensure that doctors don't have to factor in price when prescribing a dose to their patients, says Marjorie Powell, assistant general counsel at Pharmaceutical Research and Manufacturers of America, the industry's Washington-based trade group.

In developing their list of medicines suitable for splitting, Dr. Stafford and his colleague sought those with characteristics making them particularly easy to break in half, such as pills that are scored. They eliminated 125 drugs that either came only in one dose, were available only in a capsule, were prepackaged or weren't available in pills at all. These criteria eliminated such drugs as the heartburn remedy Prilosec, the osteoporosis pill Evista and common asthma medications that are dispensed in inhalers.

An additional 61 pills were eliminated because the potential cost savings to be derived from splitting weren't worth the effort; 31 others were ruled out because they were time-release formulations or out of concern of adverse consequences if dosage varied to any significant extent.

"It's important for both consumers and managed-care organizations to note that pill-splitting is a strategy that needs to be used selectively," Dr. Stafford says.

The drug-industry group challenges the strategy. Ms. Powell says she isn't convinced consumers are able to accurately split pills and that symptoms of heart disease and depression often require diligent efforts to get patients on the right dose of the right drug -- something splitting the medicines could undermine.

"It clearly isn't consistent with Food and Drug Administration labeling because you don't know exactly what dose the patient is getting," she says. If a doctor urged any of her family members to consider splitting their pills, she says, "I would make sure (they) changed doctors."

At Kaiser, Tony Barrueta, senior counsel, says officials remain confident in the clinical and economic wisdom of pill splitting despite the lawsuit. "You have to do it right," he says. "But it just makes a lot of sense."

Posted on Sun, Sep. 29, 2002

Splitting pills considered as way to cut costs

By TONY PUGH
Knight Ridder Newspapers

WASHINGTON - In the scramble to cut rising prices for prescription drugs, consumers and insurers are taking a new look at an old but controversial practice - splitting pills in half.

Purchasing large amounts of medications in high doses and cutting them in half saves money because bigger-dose pills of many drugs often sell for the same price or only slightly more than smaller doses.

Consumers can purchase 30 10-milligram doses of the antidepressant Paxil for $72.02 at Drugstore.com, for example. The site sells the same number of 20-milligram doses for $76.80. Cost-conscious customers can buy the larger-dose pills, split them in half and get twice as much medication for $4.78 more.

Pill splitting is not without risks. Because they may suffer from physical, mental or emotional problems, not all patients can correctly split their pills.

And not all pills should be split. Some must remain intact to be absorbed properly. Others can't be split accurately because of their shape. Even tablets with scores - those small grooves down the center - don't always split evenly, which could result in over- and under-dosing.

But with prescription-drug spending projected to jump 13.5 percent this year to $161 billion, health-care plans are warming to pill splitting as a low-tech method to curb rising drug costs.

The Veterans Affairs Department allows pill splitting for its patients. Last week, the Illinois Medicaid program began requiring patients who take the antidepressant Zoloft to purchase higher-potency pills and split them in half. Since 100-milligram Zoloft tablets cost about the same as the 50-milligram pills - $2.79 vs. $2.73 - the state will reimburse pharmacies only for the higher dose.

The move will trim about $3 million off Illinois' projected $1.4 billion Medicaid drug budget, said program spokeswoman Ellen Feldhausen. Private insurers such as Kaiser Permanente, United Healthcare, Health Net and Wellpoint Health Network also have voluntary policies allowing doctors to permit pill splitting if patients approve.

"I think it's inevitable that health plans will take a closer look at this. When they do so will vary and be determined by their own needs," said Dr. Randall Stafford, a professor of medicine at Stanford University who recently studied the cost-saving potential of pill splitting.

The savings must be balanced against the risks of improper dosage. A recent study of 11 commonly split tablets found that eight, after splitting, did not meet industry guidelines for content uniformity - between 85 percent and 115 percent of the intended dose. Even scored tablets did not assure accurate dosages.

For these reasons, groups such as the American Medical Association, the American Pharmaceutical Association and the American Society of Consultant Pharmacists have opposed mandatory pill-splitting

policies by health plans.

But if the doctor, patient and pharmacist all agree that pill splitting is workable, the practice can be safe on a voluntary basis, said Susan Winckler, vice president for policy with the pharmaceutical association in Washington.

Stafford's research, which tracked prescription records on 11 drugs, found that a Massachusetts HMO with 19,000 members could have saved nearly $260,000 a year by having its clients regularly split pills. Savings ranged from 23 percent to 50 percent, depending on the medication, Stafford said.

Tom Clark, director of professional affairs for the American Society of Consultant Pharmacists, said Stafford's study overstated the cost savings and understated the risks. He said there had been no studies on the health of patients who split pills.

"Our position is that it's irresponsible to promote this practice without any studies to show it's safe," Clark said.

For years, many people have split their regular-dosage tablets with razors, knives and pill-splitting devices to stretch their prescriptions when they couldn't afford refills. Groups such as the AARP frown on the practice, because patients don't get the proper dosages.

Kaiser Permanente, an Oakland, Calif.-based HMO, has been the industry leader in splitting higher-dose pills since it adopted the practice on a patient-voluntary basis in the early `90s. In 1999, Kaiser was sued over the practice; several patients and a Kaiser physician claimed that patients were being forced to split pills. Kaiser denies the allegation. The lawsuit is expected to go to trial next year.

Dr. Charles Phillips, an emergency-care physician in Fresno, Calif., and a former Kaiser physician, is a plaintiff in the lawsuit. While working for Kaiser, Phillips said, he frequently saw patients with diabetes and hypertension whose health was harmed by inaccurately split medications. He still opposes the practice because of the potential for error.

"It's bad medicine," Phillips said. "It saves money at that moment in time, but if the patient gets worse (because of improperly split dosages) then society is losing money, because they've got to pay for the patient's care down the line."

Kaiser officials, who have continued the practice of pill splitting, said the Stanford study validated it.

"It confirms our view, which is that a well-designed tablet-splitting initiative has the potential to improve cost-effectiveness of care without impairing quality," said Tony Barrueta, senior counsel for Kaiser.

ON THE WEB

For more information about pill splitting, go to the American Society of Consultant Pharmacists Web site, at www.ascp.com/public/pr/policy/tabletsplitting

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Half Tablet Program – Effective August 15, 2006
FREQUENTLY ASKED QUESTIONS

Q1: What medications are available for tablet splitting in the Half Tablet Program?

The list of medications available for tablet splitting includes:

Category	Medications	Dosage
ACE inhibitors	Aceon Mavik Univasc	2mg, 4mg 1mg, 2mg 7.5mg
Angiotensin Receptor Blockers (ARBs)	Atacand Avapro Benicar Cozaar Diovan	4mg, 8mg, 16mg 75mg, 150mg 20mg 25mg, 50mg 40mg, 80mg, 150mg
Antidepressants	Lexapro Pexeva Zoloft*	25mg, 50mg 10mg, 20mg 5mg, 10mg
Lipid-lowering medications	Crestor Lipitor Pravachol* Zocor*	5mg, 10mg, 20mg 10mg, 20mg, 40mg 5mg, 10mg, 20mg, 40mg
Antivirals	Valtrex	500mg

* Half Tablet Program applies to the generic equivalents to these brands.

The list of medications available for tablet splitting does not include all medications within a therapeutic class; only those medications determined to be appropriate for splitting are included.

Some of the tablets included in this program are not scored or designed specifically to be split. However, with the use of a tablet splitter, these medications may be appropriately divided. As is true with all medical decisions, you and your doctor will need to determine if the Half Tablet Program is right for you. Medications in the program will be reviewed periodically; additional medications may be included as appropriate.

Q2: What are the criteria for determining which medications are included in the program?

The UnitedHealthcare National Pharmacy and Therapeutic (P&T) Committee approved the following clinical criteria to determine prescription product inclusion in the Half Tablet Program.

- Medications with a wide margin of safety so that minimal differences in tablet sizes will not result in either underdosing or overdosing
- Tablets that can be split relatively evenly without crumbling
- Medications that will remain stable after splitting

In addition, the medication must be available in "double" dosage strengths that are comparably priced.

The National P&T Committee approved the following criteria for exclusion of medications from the program.

- Enteric-coated tablets
- Capsules, liquids, topical medications
- Unscored extended-release tablets
- Combination tablets in which the amount of one active ingredient changes from one tablet to the next, but the amount of the other ingredient does not

Q3: How do I get my free tablet splitter?

You can call 1-877-471-1860 or visit www.halftablet.com to order your free tablet splitter and to view Frequently Asked Questions regarding the Half Tablet Program. Notification letters will contain a Participant Code which is required when ordering the tablet splitter.

Q4: How long does it take for my splitter to arrive?

Your splitter should arrive within 10 business days. Please do not call to check on the status of your tablet splitter until at least 10 business days. If you do not receive your splitter after 10 business days you may call 1-877-471-1860 for more information.

Q5: Can I still get a free tablet splitter if I don't have a Participant Code?

If you haven't received a letter, lost your letter, or do not have a Participant Code you can still receive one free tablet splitter by calling 1-877-471-1860. You will be asked to provide your UnitedHealthcare member number and your eligibility in the program will be verified. Not having a Participant Code may cause a delay in receiving your free tablet splitter.

Q6: What if lose my tablet splitter? What if it breaks or wears out?

Tablet splitters are available for purchase at most pharmacies. UnitedHealthcare will provide you with one free tablet splitter.

Q7: How does the program work?

If you fill a prescription for a medication included in the Half Tablet Program you will:

- Receive a notification letter in the mail informing you of the Half Tablet Program.
- Discuss the Half Tablet Program with your doctor. You and your doctor decide together if the program is appropriate for you. If yes, your doctor writes a new prescription for the higher-strength dosage with instructions to take one-half tablet.
- Fill your prescription at a participating retail pharmacy.
- Receive an appropriate quantity (15 tablets to meet 30-day supply, 16 tablets to meet 32-day supply, or 17 tablets to meet 34-day supply) with instructions for using half a tablet.
- Follow instructions included in member notification letter for obtaining free tablet splitter or purchase one at a retail pharmacy.

Q8: How does the Half Tablet Program work at mail order?

You will receive 45 tablets to meet a 90-day supply at mail order. Because prescriptions are dispensed as written through mail order, you must obtain an appropriately written prescription for participation. The mail order pharmacy will not make outbound patient or doctor calls to initiate program participation.

Q9: What if I don't want to participate in the program?

Participation in the program is entirely voluntary. If you do not wish to participate in the program, you may simply continue to fill your prescription as usual, taking the same strength dosage. No action is required if you choose not to participate. If you try the Half Tablet Program and decide that it is not right for you, you may have your doctor write a new prescription for the old dosage level and go back to your usual copay.

Q10: Have any studies been done on the safety and effectiveness of tablet splitting?

A number of clinical studies have been conducted on the safety and effectiveness of tablet splitting. These studies, published in peer reviewed medical literature, conclude that when appropriate medications are selected, tablet splitting delivers a safe and effective dose of medication. The following sections summarize two of the studies that have been conducted (please be advised the descriptions below are very clinical in nature).

Parra D et al. Effect of splitting simvastatin tablets for control of low-density lipoprotein cholesterol. American Journal of Cardiology 2005;95:1481-1483.
This is a retrospective evaluation of a voluntary simvastatin tablet splitting program in 6 VA medical centers. A total of 1,331 patients who were converted to split tablets and 2099 who were not converted were included in the analysis. Patients were converted from whole to split simvastatin tablets at the same total daily dose and issued a pill splitter and instructions about the conversion. Patients who had visual limitations or other disabilities were exempted from the conversion as were patients whose health care provider or pharmacist deemed them unable to perform the tablet splitting. Primary endpoints were the average final LDL-cholesterol value and the average change from baseline between the split group and the whole tablet group. Secondary endpoints included comparison of total yearly simvastatin costs between groups, incidence of transaminase increases greater than 2 to 3 times the upper limit of normal and assessment of compliance. Baseline and final LDL-cholesterol levels and average change from baseline were not significantly different between

groups (P>0.05), nor were the incidences of transaminase increases or measurements of patient compliance.

Gee M, Hasson NK, Hahn T, and Ryono R. Effects of a tablet-splitting program in patients taking HMG-CoA reductase inhibitors: analysis of clinical effects, patient satisfaction, compliance, and cost avoidance. Journal of Managed Care Pharmacy. 2002(8)6:453-58.
The primary objective of this study was to determine the effect of splitting atrovastatin, lovastatin, and simvastatin tablets on laboratory outcomes (lipid panel and liver enzyme tests). Other objectives were to assess patient compliance and satisfaction with splitting tablets and to measure the reduction in drug acquisition cost. Before entering the program, patients were evaluated by a prescribing physician or pharmacist for cognitive or physical barriers to assess whether or not hey were able to effectively split tablets. If patients agreed to participate, prescriptions were automatically converted by a pharmacist. A tablet splitter and instructions for use were provided free of charge to patients. A total of 2,019 patients were included in the trial conducted by a Veterans Affairs Health Care System facility. A total of 512 patients were eligible for the laboratory analysis. There was no difference between preintervention and postintervention laboratory values for total cholesterol and triglycerides. There was a statistically significant, but not clinically significant decrease in LDL (102 vs. 97, p<0.001) and increase in HDL (46 vs. 48, p<0.001), AST (26 vs. 28, p<0.001) and ALT (24 vs. 26, p<0.006) after the initiation of tablet splitting. A total of 454 patients responses to a mailed questionnaire (50%). Results showed that 84% believed that the tablet splitter was not difficult to use, 85% stated that split tablets were not harder to take compared to whole tablets, and 74% agreed that the tablet splitter was not too time-consuming or bothersome; 46% believed that it was easier to take medications when they did not have to split the tablets. Only 7% of the patients stated that tablet splitting had an effect on their willingness to take medications, and 7% stated that they missed more doses in a month while tablet splitting.

Other studies on tablet splitting include:

1. MA Veronin and B Youan. Magic bullet gone astray: medications and the internet. Science 2004: 305:481.
2. JM Rosenbergy et al. Weight variability of pharmacist-dispensed split tablets. J Am Pharm Assoc 2002; 42:200.
3. J Teng et al. Lack of medication dose uniformity in commonly split tablets. J Am Pharm Assoc 2002; 42:195.
4. JE Polli et al. Weight uniformity of split tablets required by a Veterans Affairs policy. J Manag Care Pharm 2003; 9:401
5. TJ Cook et al. Variability in tablet fragment weights when splitting unscored cyclobenzaprine 10 mg tablets. J Am Pharm Assoc 2004; 44:583
6. BT Peek et al. Accuracy of tablet splitting by elderly patients. JAMA 2002; 288:451
7. MC Duncan et al. Effect of tablet splitting on serum cholesterol concentrations. AM Pharmacother 2002; 36:205.
8. M Gee et al. Effects of a tablet-splitting program in patients taking HMG-CoA reductase inhibitors: analysis of clinical effects, patient satisfaction, compliance, and cost avoidance. J Managed Care Pharm 2002; 6:453.
9. JP Rindone. Evaluation of tablet-splitting in patients taking lisinopril for hypertension. JCOM 2000; 7:22.
10. RS Staffor and DC Radley. The potential of pill splitting to achieve cost savings. Am J Manag Care 2002; 8:706.
11. P Gupta and K Gupta. Broken Tablets: does the sum of the parts equal the whole? Am J Hosp Pharm 1988; 45:1498.
12. JT McDevitt et al. Accuracy of tablet splitting. Pharmacotherapy 1998; 18:193.

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View a list of Frequently Asked Questions for UnitedHealthcare's Half Tablet Program.

You need Adobe Reader installed on your computer in order to view the Frequently Asked Questions. If you do not have it, you may click below for a free download.

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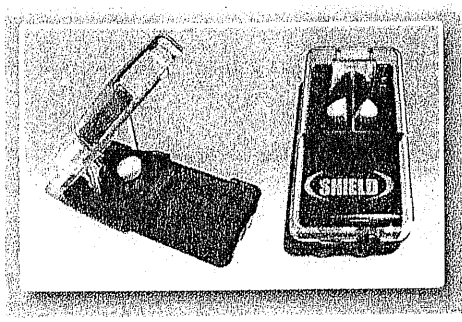

To order your FREE tablet splitter as part of the UnitedHealthcare Half Tablet Program simply type in the Participant Code and your name as it appears on your Half Tablet Program notification letter and click submit. Only one tablet splitter per participant.

Participant Code | First Name | Last Name

Submit

☐ I have read and acknowlege the statement below

United Healthcare Services, Inc. ("United") is providing this free tablet splitter to you at your request. By ordering this tablet splitter, you acknowledge and agree that you will only use it to split tablets that your doctor has approved for splitting.

To help maintain the effectiveness of your medication, do not split all of your tablets at one time. Split one tablet and take one half. Take the second half for your next scheduled dose. Repeat the process until you have taken all of your medication.

This tablet splitter is not manufactured by United or any of its affiliates. United makes no warranty as to the reliability of the tablet splitter, nor does United guarantee or warrant the performance of the tablet splitter, including the tablet splitter's conformity to any law, rule, regulation or policy. You assume full responsibility for using the tablet splitter for its intended use in accordance with the manufacturer's instructions. United is not responsible for any direct, indirect incidental, consequential or punitive damages arising out of your use of this tablet splitter.

THE WALL STREET JOURNAL. ONLINE

August 30, 2002

HEALTH

Study Finds Splitting Pills Usually Safe, Saves Money

By RON WINSLOW
Staff Reporter of THE WALL STREET JOURNAL

The practice of splitting pills to save money on prescription drugs could lead to significant cost savings without risking the effectiveness of the medicines or the safety of patients, researchers say in a new study.

But doctors, health plans and patients should limit the practice to pills that, for both their price and the way they are made, lend themselves to it.

Drug prices are spiraling out of control. Read the series of Page One stories[1] on the embattled pharmaceutical industry.

HEALTH INDUSTRY EDITION

For more health coverage, visit the Online Journal's Health Industry Edition at wsj.com/health[2], and take a tour[3] of the edition.

"You need to make sure it's done accurately, with full discussion between patients and physicians," says Randall Stafford, assistant professor of medicine at Stanford University's Center for Research in Disease Prevention and lead author of the study, which appears in the current issue of the American Journal of Managed Care. That being said, pill-splitting "can provide cost savings without really changing the clinical care that patients are getting," Dr. Stafford says.

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Write to Ron Winslow at ron.winslow@wsj.com[4]

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(4) mailto:ron.winslow@wsj.com

Updated August 30, 2002

RS

Effect of Tablet Splitting on Serum Cholesterol Concentrations

Megan C Duncan, Sharon S Castle, and Daniel S Streetman

clinical outcomes

OBJECTIVE: To evaluate the effects of tablet splitting on low-density lipoprotein (LDL) cholesterol and total cholesterol values in patients taking simvastatin and atorvastatin.

DESIGN: A retrospective chart review of total cholesterol and LDL cholesterol values of patients instructed to split simvastatin or atorvastatin between January 1999 and November 2000.

SETTING: Veterans Affairs Medical Center in Huntington, WV.

PATIENTS: Patients were included if they were taking simvastatin or atorvastatin with regular lipid management and follow-up laboratory results. Patients were required to remain on the same milligram-per-day dose at least 6–8 weeks before and after tablet-splitting initiation and have cholesterol values drawn at least 6 weeks after initiation of both whole-tablet and half-tablet dosing. Patients were excluded if they had a triglyceride level >400 mg/dL or were noncompliant on the basis of pharmacy records and provider notes.

MEASUREMENT OUTCOMES: The primary end points were changes in total cholesterol and LDL cholesterol values before and after the patient was switched to half-tablet therapy.

RESULTS: The overall results for this review demonstrated no statistically significant increase in total cholesterol and LDL cholesterol concentrations. Total cholesterol and LDL cholesterol values actually decreased from presplitting to postsplitting, $p = 0.017$ and $p = 0.003$, respectively.

CONCLUSIONS: The investigation showed that half-tablet dosing was as effective as whole-tablet dosing. The program will be continued as a part of quality patient care at the Huntington Veterans Affairs Medical Center.

KEY WORDS: atorvastatin, LDL cholesterol, simvastatin, tablet splitting, total cholesterol.

Ann Pharmacother 2002;36:205-9.

Tablet-splitting programs have been implemented by a variety of managed care organizations to decrease the cost of high-volume medications. The pharmaceutical industry discourages tablet splitting, claiming a possible lack of homogeneity when manufacturing tablets, especially if unscored. Patient acceptance and compliance with tablet-splitting programs have also been areas of concern.

Existing data regarding this treatment approach are sparse and inconclusive. Rindone[1] investigated the efficacy of lisinopril in the treatment of hypertension before and after tablet splitting. Twenty-nine patients were enrolled from the Veterans Affairs (VA) Medical Center in Prescott, AZ. Patient response to tablet splitting was evaluated by use of a crossover design, where patients received a full tablet for 2 weeks and a split tablet for 2 weeks. The full-tablet and split-tablet systolic and diastolic mean blood pressure values were compared. All values remained stable throughout the study, with no statistically significant differences noted between full-tablet and split-tablet treatments. Others have reported both positive and negative results in regard to tablet splitting in relationship to patient compliance, accuracy of splitting, and cost-effectiveness associated with similar programs.[2]

The tablet-splitting program at the Huntington VA Medical Center was started in January 1999 to aid in the control of the pharmacy budget by targeting high-cost, high-volume medications. Medications included in the program are lisinopril, irbesartan, simvastatin, atorvastatin, lovastatin, citalopram, nefazodone, paroxetine, mirtazapine,

Author information provided at the end of the text.

sertraline, risperidone, venlafaxine, rofecoxib, sumatriptan, and sildenafil.

Upon implementation of this program, it was important to ensure patient satisfaction and quality of care as well as cost-effective therapy. A patient satisfaction survey was conducted prior to this investigation to determine patients' opinions regarding the tablet-splitting program.[3] On the basis of a 61% survey return rate, the majority of patients responded favorably toward the tablet-splitting program. No questions received a <70% favorable response, ranging from 70% to 90.6%. Not receiving a tablet splitter and inadequate instructions for use were the most common reasons for dissatisfaction among the returned surveys. After analyzing the results from the patient satisfaction survey, it was decided that the next step in evaluating the program was to investigate the therapeutic outcomes of tablet splitting.

The hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors, simvastatin and atorvastatin, were the target of this retrospective review. These agents were chosen because of their objective laboratory monitoring values, including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Simvastatin is the formulary HMG-CoA reductase inhibitor at the Huntington VA Medical Center. Atorvastatin use at the Huntington VA Medical Center is restricted to intolerance of simvastatin or failure of maximum dose simvastatin. Because of these formulary restrictions, the majority of patients in this investigation were receiving simvastatin.

The purpose of this study is to investigate whether the tablet-splitting program at the Huntington VA Medical Center maintains quality cholesterol management. This study will determine whether half-tablet dosing is as effective as whole-tablet dosing on the basis of total cholesterol and LDL cholesterol values drawn before and after implementation of a tablet-splitting program.

Methods

STUDY DESIGN

A retrospective comparison of total cholesterol and LDL values before and after tablet-splitting initiation was conducted by use of data gathered from a chart review of patients being treated with simvastatin or atorvastatin for primary or secondary prevention at the VA Medical Center in Huntington, WV. The study protocol was reviewed and approved by the Investigational Review Board and the Research and Development Committee of the VA Medical Center, Huntington, WV.

PATIENT SELECTION

Pharmacy records were reviewed to identify patients switched to tablet splitting between January 1999 and November 2000. Patients were included if they were on simvastatin or atorvastatin therapy with regular lipid management and follow-up, defined as monitoring of cholesterol values by providers at least every 6 months. Patients needed to remain on the same milligram-per-day dose at least 6 weeks before and after tablet-splitting initiation and have total and LDL cholesterol values drawn at least 6 weeks after whole-tablet and half-tablet dosing. Patients were excluded if they were noncompliant or had triglyceride values ≥400 mg/dL.[4-6]

Noncompliance was defined as missing medication for more than 5 doses in a week or unexplained gaps in refills. This was indicated by pharmacy refill records and provider notes. All patients received tablet splitters at no cost, because it is the policy of our institution to provide a tablet splitter to patients who are required to split tablets.

OUTCOMES

The primary end points of this investigation were changes in total cholesterol and LDL cholesterol values. On the basis of a literature search of cholesterol-lowering clinical trials, a change in total cholesterol and LDL cholesterol values ≥10% was determined to be clinically significant.[7-10] Secondary end points included changes in HDL cholesterol and triglyceride values, the use of concurrent cholesterol-lowering agents and medications affecting cholesterol values, thyroid-stimulating hormone (TSH) values, hemoglobin A_{1c} (HbA_{1c}) values, dosage increases after tablet splitting, and evaluation of National Cholesterol Education Program (NCEP) LDL cholesterol goals.[11]

POST HOC ANALYSIS

A post hoc analysis was conducted after the initial results were reported. Data from additional atorvastatin patients were added, and the data analysis was repeated for comparison with the original results. This was done to clarify whether there was a relationship between the small atorvastatin sample size and the significant increase in total cholesterol values. The post hoc analysis also included the comparison of simvastatin and atorvastatin results as additional end points.

STATISTICAL ANALYSIS

Statistical calculations were performed by use of SPSS for Windows release 10.0.5 (Chicago, IL). An a priori estimate of the minimum required sample size was performed on the basis of the results of pilot data gathered from a population of veterans receiving statin therapy that yielded an LDL mean ± SD of 115 ± 20 mg/dL. Using these data with published equations, a minimum of 50 subjects would be required to detect an 8% difference in LDL concentrations after tablet splitting with 90% power at $\alpha = 0.05$. Results were analyzed by use of multiple statistical tests. The paired *t*-test was used to evaluate differences between continuous presplitting and postsplitting data. Differences in response to splitting within the simvastatin and atorvastatin groups were examined by use of the Wilcoxon signed-rank test. McNemar's test was used to compare paired categorical data, and χ^2 analysis was used for comparisons of nonpaired categorical data. All tests were two-tailed, and results were considered statistically significant if the p values were ≤0.05.

Results

A total of 125 patients who were switched to tablet splitting between January 1999 and November 2000 were identified. Sixteen patients were excluded because of triglyceride values >400 mg/dL. This left 109 patients who met both the inclusion and exclusion criteria (93 simvastatin, 16 atorvastatin), allowing their data to be entered in the study. Baseline patient demographics prior to splitting tablets are listed in Table 1.

The primary end points were changes in total cholesterol and LDL cholesterol values before and after the patient was switched to half-tablet therapy. Overall, the results demonstrated no statistically significant change in total cholesterol and LDL cholesterol values (Table 2) with tablet splitting. In fact, total and LDL cholesterol decreased significantly from presplitting to postsplitting ($p = 0.005$ and $p = 0.004$, respectively). When broken down into percentage of increase or decrease from baseline, a

clinically significant increase in total cholesterol values, as defined by a ≥10% increase, was demonstrated in 15% of patients overall. Thirty percent experienced a <10% increase in total cholesterol values, and 55% experienced either no change or a decrease in their values. Clinically significant increases in LDL cholesterol, as defined above, were detected in 18% of the total patients. Twenty percent had a <10% increase in LDL cholesterol, and 62% experienced either a decrease or no change in LDL values.

The overall results were separated into simvastatin and atorvastatin treatment groups (Table 3). The simvastatin group paralleled the overall results, with a statistically significant decrease in both total cholesterol and LDL cholesterol values ($p = 0.001$ and $p < 0.001$, respectively; $n = 93$). The atorvastatin group, on the other hand, showed increases in total cholesterol and LDL ($p = 0.049$ and $p = 0.098$, respectively; $n = 16$). The small number of atorvastatin patients was thought to have contributed to this significant increase; therefore, 16 atorvastatin patients were added to increase the sample to 32 patients. Patient demographics for the post hoc analysis were similar to the original sample. The results of this post hoc analysis also revealed an increase in both total cholesterol and LDL cholesterol values with tablet splitting, but the differences were not statistically significant ($p = 0.620$ and $p = 0.722$, respectively).

Other measurable secondary end points included changes in HDL cholesterol and triglycerides, as well as the number of patients with dosage increases after postsplitting cholesterol results (Table 2). HDL cholesterol demonstrated a small increase between pre- and postsplitting, but the difference was not statistically significant ($p = 0.344$). Triglyceride values showed similar results, with a small, nonsignificant decrease observed between pre- and postsplitting ($p = 0.192$). According to provider notes and pharmacy records, 16.5% (18 of 109) of patients had a dosage increase after postsplitting cholesterol values were reported. Of the 18 patients, 12 were not at NCEP (Adult Treatment Panel III) LDL cholesterol goal at presplitting baseline.[11] During the post hoc analysis, patients' cholesterol values were examined to determine whether patients were at NCEP LDL cholesterol goal. Sixty percent of patients (65/109) were at NCEP goal at presplitting baseline, and 62% of patients (67/109) were at goal postsplitting. Eighty-two percent (53/65) of those at goal presplitting remained at goal postsplitting, and 32% (14/44) of those not at goal presplitting were at goal postsplitting.

Data were collected for the other secondary end points: the use of concurrent cholesterol-lowering agents and medications affecting cholesterol values, TSH values, HbA_{1c} values, dosage increases after tablet splitting, and evaluation of NCEP LDL cholesterol goals. However, this information has been omitted because of a lack of data to sufficiently analyze the effects of these end points on the overall study outcome.

Table 1. Baseline Patient Demographics

Variable	Results[a]		
	Simvastatin	Atorvastatin	Overall
Number	93 (85.3)	16 (14.7)	109
Age (y)	65.0 ± 9.7	63.1 ± 10.3	64.7 ± 9.8
Male gender	89 (95.7)	16 (100)	105 (96.3)
TC (mg/dL)	190.3 ± 34.9[b]	171.8 ± 27.0[b]	187.6 ± 34.4
LDL (mg/dL)	113.8 ± 26.8[c]	99.1 ± 25.6[c]	111.6 ± 27.0
At NCEP LDL goal	54 (58.1)	11 (68.8)	65 (59.6)

LDL = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program; TC = total cholesterol.
[a]As mean ± SD or n (%) as appropriate.
[b]$p = 0.023$ by Student's *t*-test for baseline TC in patients receiving simvastatin vs. those receiving atorvastatin.
[c]$p = 0.048$ by Student's *t*-test for baseline LDL in patients receiving simvastatin vs. those receiving atorvastatin.

Table 2. Effects of Tablet Splitting on Lipid Parameters

Variable	Results[a]		p Value[b]
	Presplitting	Postsplitting	
TC (mg/dL)	187.6 ± 34.4	179.7 ± 32.4	0.005
LDL (mg/dL)	111.6 ± 27.0	105.1 ± 25.4	0.004
HDL (mg/dL)	40.1 ± 8.2	40.7 ± 8.2	0.344
Triglycerides (mg/dL)	178.4 ± 86.2	169.8 ± 74.8	0.192
At NCEP LDL goal	65 (59.6%)	67 (61.5%)	0.845

HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program; TC = total cholesterol.
[a]As mean ± SD or n (%) as appropriate.
[b]According to paired *t*-test or McNemar's test as appropriate.

Discussion

The purpose of this retrospective chart review was to determine whether the quality of patient care was maintained after implementation of a tablet-splitting program. This program has been estimated to reduce cost at the VA Medical Center in Huntington, WV, by $750 000 each

Table 3. Effects of Tablet Splitting According to HMG-CoA Reductase Inhibitor Received

Variable	Presplitting[a]	Postsplitting[a]	p Value[b]
Simvastatin users (n = 93)			
TC (mg/dL)	190.3 ± 34.9	179.2 ± 32.9	0.001
LDL (mg/dL)	113.8 ± 26.8	104.3 ± 25.4	<0.001
Atorvastatin users (n = 16)			
TC (mg/dL)	171.8 ± 27.0	182.4 ± 30.0	0.049
LDL (mg/dL)	99.1 ± 25.6	109.4 ± 25.9	0.098
Post hoc atorvastatin users (n = 32)			
TC (mg/dL)	171.6 ± 26.6	173.0 ± 29.3	0.620
LDL (mg/dL)	97.6 ± 24.8	100.2 ± 24.6	0.722

HMG-CoA = hydroxymethylglutaryl–coenzyme A; LDL = low-density lipoprotein cholesterol; TC = total cholesterol.
[a]Results presented as mean ± SD.
[b]According to Wilcoxon signed-rank test.

year. The overall results demonstrate not only the absence of any negative effects of tablet splitting on cholesterol values but actually a statistically significant decrease in both total cholesterol and LDL cholesterol values with tablet splitting. In addition, no significant differences in HDL cholesterol or triglyceride concentrations were observed after tablet splitting, further illustrating the effects of that activity.

Factors that might have influenced the results and/or contributed to the observed decrease in cholesterol values may be patient compliance, tablet shape, lifestyle modifications, and length of therapy. The small atorvastatin sample size may have been a factor in the initial increase observed in total and LDL cholesterol concentrations in patients who received atorvastatin.

One possible explanation of these results is that patients may have become more compliant with half-tablet medications. This could be due to a higher patient awareness and/or responsibility to ensure that their medication is split before taking it. There was also some evidence of this during the patient satisfaction survey at the Huntington VA Medical Center, which surveyed many of the same patients included in this review.[3] According to the results of the survey, 11% of patients stated that they missed fewer doses of the split medication compared with other whole-tablet medications. However, 21% of patients reported that they had missed more half-tablet doses than whole-tablet. In a similar report on patient satisfaction, 34.7% of 150 patients reported that they missed "many fewer" doses of the split medication compared with other whole-tablet medications.[12] Only 6% of patients in that study reported missing "more" to "many more" doses of the split tablets. A survey by Fawell et al.[13] showed that 5% of 57 patients missed "a few less" split tablets than whole tablets, whereas 17% of patients reported missing "a few more" to "many more." With regard to compliance, the possibility that patients took a whole tablet by mistake, thereby decreasing their cholesterol values further, should also be taken into consideration. According to the patient satisfaction survey at the Huntington VA Medical Center, 9% of patients took a whole tablet by mistake at least 3 times or more per month.[3] A prospective review could provide a more controlled monitoring process of patient compliance, thus validating patients' reports of half-tablet compliance. Because the end points described in this study were objective measures, the monitoring of compliance would not be expected to significantly change the results but may explain how the results transpired.

The shape of the tablet could have influenced patient compliance and may explain the observed differences in lipid response according to the statin received. Patients may be able to split certain shapes of medication more easily than others. Simvastatin and atorvastatin have different shapes for different strengths of tablets. If patients receiving atorvastatin found those tablets more difficult to split, or if those tablets split less evenly, the resulting difficulty in consuming the prescribed dose may explain at least some of the findings described herein.

Lifestyle modifications were not taken into consideration during the review. Many patients had cholesterol values spaced as far apart as 6 months, leaving room for exercise improvement, smoking cessation, and weight loss. All of these variables may beneficially affect patients' cholesterol values independently of cholesterol-lowering therapy. A prospective trial may be able to follow patient lifestyle changes over a period of time, to allow analysis as a confounding factor in cholesterol-lowering therapy.

Simvastatin is the formulary HMG-CoA reductase inhibitor at the Huntington VA Medical Center; therefore, the majority of patients in this investigation were on simvastatin. Because of the formulary restrictions requiring atorvastatin to be reserved for failure of simvastatin, most patients on atorvastatin have been on cholesterol-lowering therapy longer and may have been more difficult to treat than patients taking simvastatin. This may contribute to the observed decreases in cholesterol values for patients taking simvastatin compared with the increases in patients taking atorvastatin. The theory supporting this may be that patients taking simvastatin are just beginning cholesterol-lowering therapy and may still be heading toward steady-state and the LDL cholesterol goal. The patients taking atorvastatin, who tend to be more difficult to treat, may have been on cholesterol-lowering therapy longer, advancing them closer to steady-state, therefore producing less decrease or fluctuation in cholesterol values.

Atorvastatin use at the Huntington VA Medical Center is restricted to intolerance of simvastatin or failure of maximum dose simvastatin. The population of patients receiving atorvastatin at the Huntington VA Medical Center is substantially less than simvastatin; therefore, a smaller sample size does represent the overall VA atorvastatin population. According to the post hoc analysis, it is possible that the small sample size may have contributed to some of the observed significance in the increased total cholesterol values; however, even with 32 patients in the atorvastatin group, those receiving simvastatin responded substantially better to tablet splitting than those receiving atorvastatin. Additional studies with larger and more proportional group sizes are needed to confirm these findings.

Summary

These findings demonstrate that half-tablet therapy with simvastatin and atorvastatin is at least as effective as whole-tablet therapy at favorably modifying the lipid profile. The objective of this review was to evaluate whether there was a significant increase in total cholesterol and LDL cholesterol values when patients were switched from whole-tablet to half-tablet dosing. The results showed a statistically significant decrease in cholesterol values with tablet splitting. The tablet-splitting program at the Huntington VA Medical Center has been accepted by patients and does not jeopardize quality patient care; therefore, it will continue as a cost-savings measure by the pharmacy department.

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EXTRACTO

OBJETIVO: Evaluar el efecto de partir tabletas en los niveles de colesterol total y LDL de pacientes que usan simvastatina y atorvastatina.

DISEÑO: Revisión retrospectiva de expedientes de pacientes que habían sido instruidos para que partieran tabletas de simvastatina o atorvastatina entre enero de 1999 y noviembre de 2000.

ESCENARIO: Centro Médico de la Administración de Veteranos en Huntington, West Virginia.

PACIENTES: Se incluyeron los pacientes cuyos expedientes indicaban que habían usado simvastatina o atorvastatina y tenían los resultados de laboratorios regulares y de seguimiento de niveles de lípidos. Los pacientes tenían que haber permanecido en la misma dosis (mg/d) por lo menos de 6–8 semanas antes y después de comenzar a partir las tabletas y tener niveles de colesterol obtenidos por lo menos 6 semanas después de haber iniciado la administración de la tableta completa y la mitad de la tableta. Se excluyó a aquellos pacientes que tenían niveles de triglicéridos mayores de 400 mg/dL o que no eran cumplidores con su terapia según los expedientes del departamento de farmacia y las notas de los proveedores de servicios.

MEDICIÓN DE RESULTADOS: Se midió el cambio en los valores de colesterol total y LDL antes y después de que el paciente comenzó a partir la tableta.

RESULTADOS: No se encontró un aumento estadísticamente significativo en los niveles de colesterol total y LDL entre el período antes de iniciar el programa de partir tabletas a la mitad y después de iniciado el mismo. De hecho, los niveles de colesterol total y LDL disminuyeron después que los pacientes comenzaron a partir las tabletas, $p = 0.017$ and $p = 0.003$, respectivamente.

CONCLUSIONES: El estudio demostró que la práctica de dosificar partiendo tabletas en 2 fue tan efectiva como la de dosificar a base de tabletas completas. El programa de partir tabletas continuará como parte de la atención al paciente de calidad que se ofrece en el Centro Médico de la Administración de Veteranos en Huntington.

Homero A Monsanto

RÉSUMÉ

OBJECTIF: Évaluer l'effet du fractionnement des comprimés sur le cholestérol-LDL et sur le cholestérol total chez les patients qui reçoivent de l'atorvastatine ou de la simvastatine.

DEVIS EXPÉRIMENTAL: Une analyse rétrospective des dossiers de tous les patients qui ont reçu des comprimés fractionnés (demi-comprimés) d'atorvastatine ou de simvastatine entre janvier 1999 et novembre 2000 ainsi que des valeurs de cholestérol-LDL et de cholestérol total inscrites a été faite. Le fractionnement des comprimés est réalisé dans un optique de diminution des coûts.

LIEU DE L'ÉTUDE: Un centre médical pour vétérans situé à Huntington, Virginie de l'Ouest.

PATIENTS: Les patients étaient inclus dans l'analyse s'ils recevaient de l'atorvastatine ou de la simvastatine conjointement avec un suivi du profil lipidique. Les patients ont été informés qu'ils devaient recevoir la même posologie du médicament au moins pendant 6 à 8 semaines avant le début du fractionnement des comprimés ainsi qu'après. Des mesures du cholestérol ont été faites au moins 6 semaines après le début du fractionnement ou chez les autres après 6 semaines sans fractionnement de comprimés. Les patients qui ont montré des valeurs de triglycérides supérieures à 400 mg/dL ou qui n'ont pas été fidèles à leur médication ont été exclus.

MESURE DE L'EFFET: Les mesures primaires étaient les variations dans les valeurs de cholestérol-LDL et de cholestérol total avant et après le fractionnement des comprimés mais toujours à la même posologie.

RÉSULTATS: Les résultats de cette analyse montrent qu'il n'y a pas eu d'augmentation statistiquement significative dans les niveaux de cholestérol-LDL et de cholestérol total. En fait, les niveaux de cholestérol-LDL et de cholestérol total pré-fractionnement ont diminué après le fractionnement, $p = 0.017$ et $p = 0.003$, respectivement.

CONCLUSIONS: Cette analyse montre que le traitement par l'atorvastatine ou par la simvastatine à la même posologie mais en fractionnant les comprimés (demi-comprimés) produit la même efficacité que le traitement à la même posologie mais avec un comprimé entier. Ce type d'analyse sera poursuivi dans le cadre d'un programme de qualité des soins aux patients au Centre Médical des Vétérans de Huntington.

Denyse Demers

VIEWPOINT

Tablet Splitting: Imperfect Perhaps, but Better Than Excessive Dosing

Jay S. Cohen

The important and controversial issue of tablet splitting is addressed in two articles in this issue of *JAPhA*. In a laboratory setting, Teng et al.[1] split tablets from 11 drug products, analyzed the fragments, and found that only 3 of the products split evenly enough to conform to current standards published in the *United States Pharmacopoeia* (USP) for whole tablets. Based on these findings, these researchers concluded that the general practice of splitting tablets should not be recommended.

Rosenberg et al.[2] collected and analyzed the fragments of 22 drugs that had already been split by pharmacists but were not used at long-term care facilities. These authors concluded that tablet splitting resulted in an unacceptable amount of weight variation and recommended better standards to assure uniformity of split tablets.

Although tablet splitting has become controversial lately because some health care organizations, in an effort to reduce prescription drug costs, have required patients to split tablets, the role of tablet splitting in clinical medicine stretches back many decades. There are many reasons for this. As stated in the Teng et al.[1] article, the axiom "right drug, right patient, right dose" articulates a basic goal of pharmacy practice to ensure that patients receive their medications exactly as prescribed. However, this axiom also applies to clinical practice for another reason—to better match drug doses to patients' needs and tolerances and thereby avoid dose-related adverse effects.

Doses Too Often High

Dose-related adverse effects of medications are a major problem in modern medical practice. In a 1998 issue of *JAMA*, an in-depth meta-analysis revealed that approximately 106,000 deaths and more than 2 million serious adverse effects attributable to drug therapy occur in U.S. hospitals each year,[3] making adverse drug effects one of the leading causes of death in America annually. Almost unnoticed in the debate over these statistics was a detail of the study methodology: The authors had excluded incorrect doses, equivocal cases, and medication errors from their analysis. In other words, not only were 76.2% of the identified adverse reactions dose-related, but they occurred at doses that were supposedly correct for the patient, according to standard treatment guidelines. Thus, this study was a striking reminder of the following:

1. The "correct" dose, based on drug company guidelines in package inserts, may not be correct for many patients.
2. Broad variation in drug response among patients is a common phenomenon in clinical practice.
3. Avoiding adverse effects means matching doses to patients' varying needs and tolerances.

The ability to match doses to patients depends on the availability of multiple dose sizes and adequate dose–response information. These are not always provided, so splitting of tablets or division of capsules is sometimes necessary. Prozac (fluoxetine—Lilly) was introduced initially in only one size, a 20 mg capsule. Clinicians soon discovered that many patients responded to and had fewer adverse effects with doses of 5 mg or 10 mg. This required some creative methods, as described in a 1990 article in the *Journal of Clinical Psychiatry*: "Experienced geriatric clinicians sometimes advise older patients to open the capsule and sprinkle small amounts of fluoxetine in a flavored beverage such as orange juice."[4] The patient would then drink one-fourth or one-half of the beverage each day.

Similar problems persist today. The recommended dose of Claritin (loratadine—Schering) is 10 mg for all adults, big or small, healthy or ill, with mild or severe allergy conditions, taking other medications or not.[5] This dose is also recommended for children as young as 6 years. I know several people who split Claritin tablets, not to save money, but because the full dose causes problems and the half dose works. Meanwhile, in December 2001, the Food and Drug Administration (FDA) approved Clarinex (desloratadine—Schering), the active metabolite of loratadine, also with a one-size-fits-all dosage for all adults.[6] Tablet splitting will likely be necessary again with this new medication.

Improving Safety and Adherence

The ability to practice precision dosing should also be important to manufacturers. Lotronex (alosetron—GlaxoSmithKline), highly effective for irritable bowel syndrome, was withdrawn after just 10 months on the market. Lotronex was marketed in only one strength for adults of all sizes and states of health.[7] The dose was the same, whether the case of irritable bowel syndrome was mild or severe. When patients showed early signs of constipation, a dose-related adverse effect, dose reduction might have been helpful. Instead, bowel obstructions occurred, surgeries were required, people died, Lotronex was withdrawn, and patients, physicians, and the manufacturer lost access to a highly effective medication. Another example is Seldane (terfenadine—Dow), the most prescribed antihistamine in the world from 1985 through 1995, when it was available only in a 60 mg dosage

strength. It was withdrawn because of dose-related cardiac toxicities with this dosage,[8] while a 50% lower dose was highly effective but never marketed.[9]

Precise dose adjustment is also important for maintaining adherence. Doses of Lipitor (atorvastatin—Parke-Davis; Pfizer) 5 mg reduce low-density lipoprotein cholesterol from 27% to 29%,[10] which is more than the recommended starting doses of Mevacor (lovastatin—Merck) and Lescol (fluvastatin—Novartis), but the smallest Lipitor tablet is 10 mg. Physicians sometimes instruct patients who develop adverse effects with 10 mg to split the tablet. A half-dose is often sufficient, and splitting the tablet saves the patient the high cost of purchasing another prescription.

This is not just a convenience issue. With each problem and extra cost, adherence drops. Indeed, patients often ask for permission to split tablets when a full dose causes unpleasant effects. Also, adverse effects can be reduced when a dose, prescribed once daily, is split and taken twice daily (because peak plasma levels are not as high).

Moreover, it is no coincidence that many adverse reactions occur when doses are increased. Some patients, especially those who are fragile or medication-sensitive, do not tolerate the 100% increases that are often prescribed. Tablet splitting allows more gradual increases, reducing adverse effects and ensuring adherence.

Splitting tablets is part of standard protocols for some conditions. Two brands of levothyroxine—Levoxyl (Jones) and Synthroid (Abbott)—are produced in up to a dozen strengths, all scored specifically to allow physicians to make very precise dose adjustments based on thyroid function tests. Coumadin (warfarin—DuPont) is produced in nine sizes, all scored.[11]

Furthermore, after approval, many drugs are discovered to be effective at doses lower than those manufacturers recommended.[12] In 2001 FDA veterans Carl Peck and James Cross reported that official changes in recommended doses are made for more than 20% of drugs.[13] These changes usually take years, but clinicians recognize the need for lower doses much more quickly. Many other drugs, requiring similar dose adjustments, are never officially changed. The only approved dose of Celebrex (celecoxib—Pharmacia; Pfizer) for osteoarthritis remains 100 mg twice daily for all adults, yet 50 mg twice daily is effective for many patients.[14] Knowing this, are clinicians remiss if they do not consider halving the Celebrex dose for appropriate patients? Are not patients entitled, by their right of informed consent, to know about lower, safer doses that might prove effective for them?

This is unavoidable fact: Fine-tuning of dosage is a fundamental part of optimal therapeutics, yet the limited number of dose sizes and the inability to split tablets accurately hinders such fine tuning. The result is a dilemma that affects the very heart of quality patient care.

A Glass Half Full

Looking at the specifics of the two studies in this issue, perhaps the situation is not as bad as it seems. In the Rosenberg et al.[2] study, 12 of the 22 prescriptions had no split tablets that deviated beyond the 85% to 115% range, and only 5 of the 22 products had more than 10% of their fragments beyond this range. In the Teng et al.[1] study, 3 of 11 tablets fulfilled the rigorous performance requirements, and another 5 tablets had no fragments beyond the 75% to 125% range.

Clinically, this might be good enough with some drugs, including the Lipitor 20 mg that was tested. If patients receiving a split Lipitor tablet on successive days took 12 mg, 8 mg, 14 mg, 7.5 mg, and 11 mg, would treatment be compromised? Probably not. Indeed, some physicians have patients take a whole Lipitor tablet every other day, skipping a dose altogether on in between days. Other long-acting drugs, such as proton pump inhibitors, are sometimes dosed similarly, based on pharmacodynamic considerations.

Teng et al.[1] conclude that tablet splitting is not recommended for drugs with substantial toxicity and steep dose–response efficacy curves. However, for drugs with low toxicity and relatively flat dose–response relationships, tablet splitting may not cause problems.

Rosenberg and coauthors[2] address the central problem—the lack of reliability of the tablets themselves. Some tablets, including several in these studies, such as Viagra (sildenafil—Pfizer) and Effexor (venlafaxine—Wyeth-Ayerst), seem designed to frustrate attempts at tablet splitting. Others are produced in highly irregular shapes in the interests of marketing, not medical accuracy. FDA exerts no guidelines on tablet type or shape. The solution, as Rosenberg et al.[2] suggest, is the production of tablets that, whole or split, conform to USP requirements. Accomplishing this should not be difficult. Some tablets already conform to these standards, and the best shapes have already been identified.[15]

Mandated tablet splitting, initiated by insurers, is a questionable policy. Some patients are not comfortable splitting tablets on their own, and others are unable to accomplish this task satisfactorily. Tablet cutters are cheaply made and notoriously variable in accuracy. However, elective tablet splitting in the service of determining the best dosage based on the individual responses of different patients, and in the service of preventing or minimizing dose-related adverse effects and of improving adherence, is highly important in everyday medical practice. It has a role in clinical medicine, and steps should be taken to ensure that it can be done safely and accurately.

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See related articles on pages 195 and 200.

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PHARMACY THROUGH THE AGES

National Drug Clerk

Up until the mid 20th century, the employee pharmacist was referred to as a drug clerk. Virtually all pharmacies were owned by an individual, most of whom were licensed pharmacists. Many owners would also hire another licensed pharmacist, the drug clerk. Indeed, the career pathway was clearly shown in the inaugural cover (at left) of the *National Drug Clerk*, the publication of the National Association of Drug Clerks.

The National Association was incorporated in Columbus, Ohio, in 1910. The stated objective of both the association and the journal was to further pharmaceutical education and progress, professional and scientific advancement, and to encourage such relations between the drug clerk and employer as would promote their mutual interests and welfare.

Dennis B. Worthen, PhD, Lloyd Scholar, Lloyd Library and Museum, Cincinnati, Ohio.

Photo courtesy of the Lloyd Library and Museum.

Press Release Source: Stanford University Medical Center

Pill-Splitting Can Yield Cost Savings On Common Prescription Drugs, Stanford Researchers Find

Thursday August 29, 7:01 pm ET

STANFORD, Calif.--(BUSINESS WIRE)--Aug. 29, 2002--Squeezed by the rising cost of prescription drugs, health plans and other health-care organizations are pursuing cost-saving strategies such as encouraging the use of generics, using narrowly tailored drug formularies and implementing multi-tiered co-payment systems.

Now, researchers at Stanford University Medical Center have confirmed that a less-common strategy -- pill-splitting -- could yield significant cost savings without compromising drug efficacy or safety. They emphasize that pill-splitting must be implemented with careful controls and begin with a doctor-patient conversation.

"When properly implemented, pill-splitting can be a safe, viable cost-saving strategy," said Randall Stafford, MD, PhD, a researcher at the Stanford Center for Research in Disease Prevention and lead author of an article published in the August issue of the American Journal of Managed Care. "Physicians should consider using pill-splitting with selected medications and patients, and patients may want to bring it up with their doctors."

Many prescription drugs are available at increased dosages for the same or similar costs as smaller dosages. When physicians prescribe half as many higher-strength pills and have the patient split them to achieve the desired dosage, the cost of certain medications can be reduced as much as 50 percent.

Using pharmacy claims data from a commercial managed-care plan in Massachusetts, Stafford and colleagues examined how often pill-splitting was used. They found the practice was relatively infrequent, accounting for annual savings of $6,200 in the health plan.

Researchers then used a systematic screening process to determine which medications were appropriate for pill-splitting. Starting with the 265 medications most commonly prescribed nationally and within the specific health plan, they narrowed the list in stages. First they eliminated drugs that came prepackaged, weren't available in tablets or were available in only one dosage. They then eliminated medications in which pill-splitting yielded savings of less than 25 percent, based on the average wholesale price. Finally, they eliminated medications in which altering the drug's physical properties could reduce its effectiveness -- such as compounds that could become chemically unstable if split.

This screening process yielded a list of 11 medications commonly used by physicians in the health plan, which the researchers determined could be split safely and effectively with significant cost savings (see chart). The average potential savings for each drug, over varying dosages, ranged from 23 to 50 percent. A patient taking a 10-mg tablet of lisinopril daily, for example, would have annual medication costs of $340. By prescribing half the number of 20-mg tablets and splitting them, medication costs would drop to $180 annually.

Friday, 13 September, 2002, 09:09 GMT 10:09 UK

Pensioner markets device to split Viagra pill

Viagra made Pfizer $150bn last year

A thrifty pensioner has come up with a way of boosting his dollars and his sex life.

Carmen Reitano, aged 70, has invented a way to split his Viagra pills.

This saves his cash on the $10 per tablet pills as well as doubling his supply of tablets.

Mr Reitano, of Massachusetts, America, now plans to market his invention, which splits the little blue anti-impotence drug into two equal portions.

Tablets

He has even set up his own website where he promised visitors that his "Revolutionary V" Viagra splitter" will cut costs by 50%.

Mr Reitano said his device is "a Godsend."

> We've gotten several hundred orders so far
>
> Carmen Reitano

He said: "Doctors are generally fully supportive of the pill splitting practice."

But he said finding out how to cut the tablets was not easy.

He said that with its odd shape of a curved top and bottom and its hard shell it had been difficult to cut with any accuracy.

And he said many had previously tried to split the pill.

'Sex is great at 78'

See also:

08 Feb 02 | Health
Viagra could go over-the-counter

02 Aug 02 | Health
Viagra 'linked to nosebleeds'

09 Aug 02 | Europe
Viagra perk story irks Europe officials

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Diet is key to avoiding cancer

Pensioner markets device to split

ORIGINAL RESEARCH

Effects of a Tablet-Splitting Program in Patients Taking HMG-CoA Reductase Inhibitors: Analysis of Clinical Effects, Patient Satisfaction, Compliance, and Cost Avoidance

MICHAEL GEE, PharmD; NOELLE K. HASSON, PharmD; TERRI HAHN, BSPharm; and RUSSELL RYONO, PharmD

ABSTRACT

OBJECTIVE: The primary objective was to determine the effect of a hydroxymethylglutaryl-CoA reductase inhibitor (HMG) tablet-splitting program on laboratory outcomes (lipid panel and liver enzyme tests). Other objectives were to assess patient compliance and satisfaction with splitting tablets and to measure the reduction in drug acquisition costs.

METHODS: Patients at a Veterans Affairs Health Care System facility were included in this study if they participated in the HMG tablet-splitting program between April and September 2000. Patients taking the same drug and dosage before and after implementation of the program were asked to complete a mailed questionnaire designed to measure satisfaction and compliance with the program. Data collected through electronic charts included patient demographics, prescribed medication, and the values for lipid panel and liver function tests.

RESULTS: A total of 2,019 patients were included in the study. The total cost avoidance achieved over one year for atorvastatin, lovastatin, and simvastatin was $138,108 (N=2,019). The majority of patients who responded to the questionnaire were satisfied and compliant with tablet splitting. In the laboratory analysis (N=512), there was no difference between prevalues and postvalues for total cholesterol and triglycerides. There was a statistically, but not clinically, significant decrease in LDL (102 versus 97, $P<0.001$) and increase in HDL (46 versus 48, $P<0.001$), AST (26 versus 28, $P<0.001$), and ALT (24 versus 26, $P=0.006$) after the initiation of tablet splitting.

CONCLUSION: Tablet splitting of HMGs had no short-term negative effects on laboratory outcomes and favorable effects on humanistic outcomes as measured by patient satisfaction and compliance. Tablet splitting of HMGs is an effective way to reduce costs and nearly double the number of patients who can be treated for the same expense.

KEYWORDS: Tablet splitting, Hydroxymethylglutaryl-CoA reductase inhibitor, Cost, Compliance, Patient satisfaction

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Tablet splitting is a practice that is becoming more popular within managed care pharmacies as the costs of medications increase. For many medications, tablet strengths are identical or similar in cost, and splitting tablets can lower the cost per dose by 40% to 50%. Tablet-splitting programs targeted at high-cost, similarly priced, and widely prescribed medications have expanded in the managed care setting to include a multitude of medications such as ACE-inhibitors (fosinopril, lisinopril, moexipril, and trandolapril), angiotensin II receptor blockers (irbesartan and losartan), Cox-2 inhibitors (rofecoxib and valdecoxib), hydroxymethylglutaryl-CoA reductase inhibitors (HMGs) (atorvastatin, lovastatin, pravastatin, and simvastatin), antidepressants (citalopram, mirtazapine, paroxetine, sertraline, and venlafaxine), carvedilol, cetirizine, metoprolol, nefazodone, sildenafil, and zafirlukast.

From previous studies, it has been shown that tablet splitting is well accepted by patients and has no effect on compliance.[1-3] Acceptance and compliance were addressed in these studies with the use of questionnaires and pill counts. One of the studies also calculated a 50% reduction in median annual acquisition cost.[2]

Two studies measured the effects of tablet splitting on clinical outcomes. The first study was a randomized, crossover trial consisting of 29 patients taking lisinopril. In this study, both groups took whole tablets for 2 weeks and split tablets for 2 weeks.[3] There was no significant difference in blood pressure between patients taking whole versus split tablets. However, this study had a small sample size, and the duration for each treatment arm was short. The second study was a retrospective chart review analysis, which evaluated the effects of tablet splitting on the lipid panels of 125 patients taking simvastatin and atorvastatin.[4] Patients were required to remain on the same dose at least 6 weeks before and after tablet-splitting initiation, and lipid panels were drawn at least 6 weeks after initiation of whole-tablet and half-tablet dosing. There was a statistically, but not clinically, significant reduction in LDL and total cholesterol levels, and no significant change in HDL and triglyceride levels. This study did not review ultimate clinical outcomes and, similar to the first study, had a small sample size.

In an effort to maximize valuable patient resources, a tablet-splitting program was implemented at the Veterans Affairs Palo Alto Health Care System in April 2000. The medications included in our program were simvastatin, lovastatin, atorvastatin, sertraline, citalopram, and lisinopril. Tablet splitting was considered a reasonable strategy for these agents because the tablets

FIGURE 1 Patient Satisfaction Questionnaire on Tablet Splitting

Directions: Please circle the most correct response (one response per question).

Which cholesterol medication do you take?
atorvastatin(Lipitor) lovastatin(Mevacor) simvastatin(Zocor)

Please describe how you take this medication:_____

1. It is easy to use the tablet splitter.
Strongly agree Agree Neutral Disagree Strongly disagree

2. The tablet splitter cuts the tablets into close-to-equal halves most of the time.
Strongly agree Agree Neutral Disagree Strongly disagree

3. How many times during the last month did the tablet splitter damage the tablet so that you were not comfortable taking the dose (one or both halves)?
Seldom 1-2 times 3-4 times 5-6 times >6 times

4. Tablets cut in half are _____ to take compared to whole tablets.
Much easier Slightly easier About the same Slightly harder Much harder

5. Tablet splitting has had no effect on my willingness to take my medication.
Strongly agree Agree Neutral Disagree Strongly disagree

6. Since I started splitting my tablets in half, I miss doses in a month.
Much more Slightly more About the same Slightly less Much less

7. How many times in the last month did you throw away a tablet (one or both halves) because you dropped it while trying to cut it or just after cutting it?
Seldom 1-2 times 3-4 times 5-6 times >6 times

8. It was much easier to take my medications when I did not have to split them in half.
Strongly agree Agree Neutral Disagree Strongly disagree

9. Using the tablet splitter is too time-consuming and/or bothersome.
Strongly agree Agree Neutral Disagree Strongly disagree

10. The use of the tablet splitter was adequately explained to me.
Strongly agree Agree Neutral Disagree Strongly disagree

11. Have you ever called the pharmacy because you had difficulty/confusion with the tablet splitter?
Yes No

12. Have you ever come to the hospital because you had difficulty/confusion with the tablet splitter?
Yes No

13. If I had to pay the full expense of my medications, I would split tablets if it could save me some money.
Strongly agree Agree Neutral Disagree Strongly disagree

Please return questionnaire in the provided envelope.

(a) are amenable to splitting (scored or easy to split), (b) are not sustained-release or enteric-coated, (c) have a flat or similar price for each strength, (d) have a wide safety margin, and (e) account for high drug expenditures.

Before entering our program, patients were evaluated by the prescribing provider or an outpatient pharmacist for cognitive and physical barriers to assess whether or not they were able to effectively split the tablets in half. The provider could request that the prescription be filled with whole tablets if that provider determined the patient to be ineligible for the tablet-splitting program. If the provider did not indicate tablet splitting in the medication order, the pharmacist would then evaluate the patient for the tablet-splitting program. The pharmacist evaluation consisted of a brief review of the patient's electronic medical record and a patient interview. If patients agreed to participate in the program, prescriptions were automatically converted by a pharmacist. A tablet splitter and instructions for use were also provided free of charge to patients. All patients were allowed to decline entry into the program upon request.

Because HMGs have objective clinical outcome measures that are consistent, easy to compare, and readily retrievable, we chose to focus our review on these agents. The primary objective of the study was to determine the effect of splitting atorvastatin, lovastatin, and simvastatin tablets on laboratory outcomes (lipid panel and liver enzyme tests). Other objectives of the study were to assess patient compliance and satisfaction with splitting tablets and to measure the reduction in drug acquisition costs.

Methods

The study was conducted in the outpatient setting of the Veterans Affairs Palo Alto Health Care System. The study was conducted in 3 phases. In Phase I, a cost-avoidance analysis was conducted. In Phase II, patient compliance and satisfaction were measured using a patient questionnaire. In Phase III, laboratory outcomes were analyzed. The study protocol was approved by the Institutional Review Board, and all patients gave written, informed consent prior to enrollment.

Phase I: Cost Avoidance

Patients were included in Phase I of the study if they were enrolled in our HMG tablet-splitting program between April 1, 2000, and September 30, 2000. The HMGs used at our institution were atorvastatin, lovastatin, and simvastatin (cerivastatin, fluvastatin, and pravastatin were not on the formulary). The patients were identified using the computerized pharmacy prescription database. To determine the cost avoidance in these patients, we obtained prescription records for HMGs in these patients over a one-year period (October 2000 to September 2001). Using the 2000-2001 VA actual drug acquisition cost for atorvastatin, lovastatin, and simvastatin, we calculated the cost of these prescriptions utilizing tablet splitting.

The calculation for cost avoidance per dose was:

Cost avoidance per dose =
Cost of whole tablet–Cost of alternative half tablet
(e.g.,=Cost of simvastatin 20 mg tablet–
1/2 cost of simvastatin 40 mg tablet)

The cost avoidance per dose was multiplied by the total amount of doses filled by all the patients. The 2000-2001 VA acquisition cost of the tablet splitters was then subtracted to calculate the overall cost avoidance.

Phase II: Patient Compliance and Satisfaction

Patients from Phase I who were on a stable dosage of an HMG for 12 weeks were enrolled in Phase II. A stable dosage was defined as no change in dosing of the HMG 6 weeks before and 6 weeks after tablet splitting was initiated. Patients were excluded prior to this phase if (a) therapy was initiated using split tablets, (b) there was a drug or dosage change at the time of conversion to tablet splitting or anytime within the 12 weeks, or (c) the patient was converted back to whole tablets within 6 weeks. Questionnaires were mailed to patients in January 2001, after the first exclusion phase, in order to measure both compliance and satisfaction with our tablet-splitting program (Figure 1). The questionnaire was adapted from the survey that was used in a prior study conducted by Carr-Lopez et al.[1] On the questionnaire, 4 questions were designed to measure satisfaction and 2 questions were designed to measure compliance. The other questions served to identify which drug was split, how it was taken, and to determine the logistics of tablet splitting. Responses were collected through April 2001.

Phase III: Laboratory Outcomes

The Phase III laboratory analysis was conducted on all patients in Phase II who had lipid panels drawn and recorded both before (prelab) and after (postlab) tablet splitting. The prelab was defined as a lipid panel taken between one year before and the day that tablet splitting was initiated. The postlab was defined as a lipid panel taken between 6 weeks and one year after tablet splitting was initiated. In patients with more than one preintervention and/or more than one postintervention lipid panel within the study period, the panel values closest to initiation of tablet splitting were used. Patients were excluded from Phase III analysis if the postintervention lab values were taken (a) within 6 weeks postconversion to tablet splitting, (b) after a drug or dosage change, or (c) if an interacting drug was initiated within 6 weeks of the lab test. Interacting drugs included cholestyramine, colestipol, cyclosporine, erythromycin, fenofibrate, gemfibrozil, nefazodone, niacin, phenytoin, antifungals (itraconazole, ketoconazole, fluconazole), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, abacavir).

To measure outcomes of tablet splitting, we evaluated lipid panels, liver enzyme tests, and creatine phosphokinase (CPK) laboratory values. Lipid panels included total cholesterol (TC),

low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG). Liver enzyme tests included aspartate aminotransferase (AST) and alanine aminotransferase (ALT). For both the lipid panels and liver enzyme tests, we compared the prelabs with the postlabs to determine if there was a change. CPK was used to identify if any patient experienced rhabdomyolysis after tablet splitting was initiated.

In a post hoc subgroup analysis, the laboratory results of dissatisfied and noncompliant patients identified from the questionnaires were compared. A dissatisfied patient was defined as anyone who had a negative response to all 4 questions that pertained to satisfaction. A noncompliant patient was defined as anyone who responded negatively to either of the questions pertaining to compliance.

Statistical Analysis

Interval data (TC, LDL, TG, HDL, AST, ALT) is presented as mean ± standard deviation, and comparisons were evaluated using the paired *t* test. For data that were not normally distributed (i.e, ALT), the data are presented as medians and compared using the Wilcoxon signed rank test. Statistical tests were performed using Sigma Stat (Version 2, Jandel, Sausalito, CA).

Results

We identified 2,019 patients enrolled in the HMG tablet-splitting program. The total cost avoidance over one year (October 2000 to September 2001) for atorvastatin, lovastatin, and simvastatin was $138,108 (Table 1), based upon actual acquisition costs for these 3 drugs.

After the cost-avoidance analysis, 1,111 patients were excluded prior to the Phase II analysis (Table 2). The remaining 908 patients were mailed questionnaires (Table 2). We received 454 responses (50%). Of the respondents, 83% were splitting simvastatin, 15% lovastatin, and 2% atorvastatin. These percentages are consistent with the overall use of these medications at our institution.

Patient satisfaction and compliance with tablet splitting were determined from the questionnaires. There were 4 questions that addressed patient satisfaction. The results of these questions showed that 84% believed that the tablet splitter was not difficult to use, 85% stated that split tablets were not harder to take compared to whole tablets, and 74% agreed that the tablet splitter was not too time-consuming or bothersome; 46% believed that it was easier to take medications when they did not have to split the tablets.

There were 2 questions that addressed patient compliance. Only 7% of the patients stated that tablet splitting had an effect on their willingness to take medications, and 7% stated that they missed more doses in a month while tablet splitting.

Five hundred-twelve patients were eligible for the laboratory analysis. The baseline demographics for these patients are listed in Table 3. The laboratory analysis showed that there was no difference between preintervention and postintervention laboratory values for total cholesterol and triglycerides (Table 4). However, there was a statistically significant decrease in LDL (102 versus 97, $P<0.001$), a statistically significant increase in HDL (46 versus 48, $P<0.001$), and statistically significant increases in both AST (26 versus 28, $P<0.001$) and ALT (24 versus 26, $P=0.006$) after the initiation of tablet splitting. No patients experienced rhabdomyolysis after tablet splitting was initiated, as determined by analysis of CPK laboratory values.

TABLE 1 Drug Acquisition Cost Avoidance*

Number of patients	2,019
Time period	October 2000 to September 2001 (1 year)
Potential drug cost (cost of whole tablets)	$352,187
Actual drug cost (cost of half tablets)	$210,768
Tablet-splitter cost	$3,311
Cost avoided	**$138,108**
Average cost avoided per patient per year	**$68.40**

** 2000-2001 VA actual drug acquisition cost for lovastatin, simvastatin, and atorvastatin was used to calculate cost avoidance.*

TABLE 2 Reasons for Patient Exclusion

Phase I Analysis (cost avoidance)	**N=2,019**
Exclusion	1,111
Therapy initiated using split tablets	726
Drug/dosage change at time of tablet split	341
Drug/dosage change within the 12 weeks	25
Patients converted back to whole tablets within 6 weeks	19
Phase II Analysis (patient survey)	**N=908**
Exclusion	396
No prelab and/or postlab	311
Postlab <6 weeks after split	11
Postlab after drug/dosage change	53
Drug interaction	21
Phase III Analysis (measure laboratory values)	**N=512**

TABLE 3 Patient Demographics (N=512)

Average age (years)	65.5±10.6
Gender	
Male	499 (98%)
Female	12 (2%)
HMG-CoA RI	
Atorvastatin	1 (0.2%)
Lovastatin	74 (14.5%)
Simvastatin	437 (85.3%)

In the subgroup analysis, the laboratory results of the dissatisfied and noncompliant (self-reported) patients identified from the questionnaires were analyzed. There was no significant change in the laboratory values between preintervention and postintervention. (Table 5).

Discussion

This study suggests that tablet splitting for HMGs has no negative effects on lipid panels or liver enzyme tests. This study is larger than the previous studies that address tablet splitting and is the first one to measure laboratory outcomes that include changes in liver enzyme tests or adverse patient events associated with splitting HMG tablets.

In the laboratory analysis, there was no change in total cholesterol and triglycerides, but there was a statistically significant decrease in LDL and a statistically significant increase in HDL. Our findings are very similar to those reported by Duncan et al.[4] The changes in LDL and HDL are most likely beneficial for the patients; however, the clinical significance and reasons for the changes are uncertain. There were also statistically significant increases in the liver enzyme tests, AST and ALT; however, these increases do not appear to be clinically significant since the levels of both the AST and ALT after the change are well within the normal range for these tests.

Among possible limitations of our study, the positive outcomes may be attributable in part to the screening process involved. Not all patients can split tablets in half effectively with a pill splitter, and, therefore, not all patients should be included in tablet-splitting programs. Patients who might be excluded from tablet-splitting programs include those with eyesight problems, arthritis in the hands, or cognitive impairment. To avoid some of these problems, outpatient pharmacists assessed the patients for both cognitive and physical barriers before initiating them in the program. If the pharmacist determined that the patient could not effectively split the tablets in half, a note was left in the patient's medication profile stating not to enter the patient into the tablet-splitting program.

Another factor that may have contributed to the favorable laboratory outcomes is lifestyle modification. While we assessed laboratory outcomes up to 12 months postsplitting, we did not give consideration to changes in weight, smoking status, alcohol consumption, or dietary modifications during that time. Any of these factors may have influenced laboratory values. In addition, our study was not designed to objectively assess medication compliance using methods such as a pill count or refill analysis. This would have been particularly useful to ensure that patients were indeed taking split tablets (and not whole tablets), which could also have affected the laboratory outcomes.

The majority of patients included in the study were satisfied and compliant with the HMG tablet-splitting program, as shown from the questionnaire results. For the few patients identified as noncompliant or dissatisfied with the program, it was important to analyze whether splitting tablets was adversely affecting their outcomes. Neither the dissatisfied nor noncompliant patients had any significant changes in their lipid panels and liver enzyme tests when comparing their laboratory values before and after tablet splitting. These results suggest that tablet splitting is also effective in these patients; however, additional results from a larger study designed a priori to specifically address this question are necessary.

The HMG tablet-splitting program reduced actual outpatient drug acquisition costs by more than $138,000 for our institution during the time period between October 1, 2000, and September 30, 2001. The cost avoidance calculated in the study for this one-year period was for all patients included in Phase I (patients converted to split tablets between April 1 and September 30, 2000). Patients who were enrolled in the program after September 30, 2000, were not included in the cost analysis. Patients continue to be successfully enrolled in the tablet-splitting program; therefore, this cost-avoidance figure is

TABLE 4 Laboratory Analysis Results (N=512)

Measure	Prelab	Postlab	*P* value
TC (mg/dL)	181±36	180±37	0.289
LDL (mg/dL)	102±28	97±29	<0.001
HDL (mg/dL)	46±12	48±12	<0.001
TG (mg/dL)	166±101	170±117	0.399
AST (U/L)	26±8	28±10	<0.001
ALT (U/L)	24±13	26±14	0.006

TABLE 5 Laboratory Subgroup Analysis Results

Measure	Prelab	Postlab	*P* value
Dissatisfied Patients (N=15)			
TC (mg/dL)	185±33	185±36	0.936
LDL (mg/dL)	107±24	107±35	0.989
HDL (mg/dL)	49±10	50±9	0.406
TG (mg/dL)	149±75	140±57	0.637
AST (U/L)	24±6	27±5	0.182
ALT (U/L)	23±9	23±8	0.976
Noncompliant Patients† (N=31)			
TC (mg/dL)	188±44	188±44	1.00
LDL (mg/dL)	104±30	103±33	0.838
HDL (mg/dL)	48±10	50±11	0.088
TG (mg/dL)	166±89	154±91	0.428
AST (U/L)	28±11	26±7	0.347
ALT (U/L)*	22	20	0.326

**Prelab and postlab are presented as median values.*
† Noncompliance was self-reported by patients as doses missed in a month after tablet splitting.

likely an underestimate of the total fiscal impact of the program over this one-year time frame. In addition, this analysis only takes into account the effect of splitting HMGs. The tablet-splitting strategy is used for a continually growing list of agents in our outpatient setting, resulting in cost avoidance of even greater magnitude. Finally, it is important to note that VA drug acquisition costs, which are considerably lower than average wholesale price, were used in our calculations. Therefore, other managed care organizations that face higher drug acquisition costs could expect a more substantial cost avoidance.

Unfortunately, due to the retrospective nature of this analysis, we were unable to precisely factor pharmacist time and effort into our analysis. These factors are, of course, very important to consider before implementing a program of this nature. If we were to assume that it took an extra 5 to10 minutes for our pharmacist to counsel and educate the 2,019 patients, it would result in an opportunity cost of 168 to 336 pharmacist hours. Still, our cost avoidance was not offset by pharmacist salary because no additional staff were employed to implement this program.

With the recent availability of generic lovastatin, many institutions may benefit foremost from converting appropriate patients requiring HMGs to lovastatin. However, because generic lovastatin is considerably more expensive than Mevacor at our institution, and it is not flat or similar priced, we continue to use the brand-name product. Furthermore, at low doses of lovastatin (10 mg and 20 mg), the dose equivalent of simvastatin is less expensive, so we continue to offer both agents.

Another possible limitation to our study was that we had to exclude a large number of patients in phase II because they did not receive a postintervention laboratory panel. However, there is nothing to suggest that the patients who did not receive a postlab would have responded to tablet splitting differently than those patients who did receive postintervention laboratory testing. This ancillary finding is nonetheless important and enables us to target provider and patient education regarding the importance of appropriate follow-up laboratory monitoring.

An additional limitation to our study was that the questionnaire was not sent to all patients. We chose not to send out the questionnaire to patients who had drug or dosage changes at the time of tablet splitting. Our goal from the questionnaire was to determine the effects of tablet splitting on patient satisfaction and compliance while taking the same drug and dosage before and after initiation of the program. We felt that satisfaction and compliance could be affected if patients were on a different medication or if they had to swallow a different size tablet. Therefore, it would not be ideal to find out how satisfied or compliant patients were with one medication or dose before splitting and compare it to another one after they started splitting. If we wanted a broader analysis to determine what patients thought of tablet splitting in general, then we could have included these patients in the questionnaire analysis as well.

The positive results from our study reinforce and expand upon the findings presented by Duncan, et al.[4] This study should be useful for many institutions and opens the door to future directions. It would be beneficial to assess outcomes of tablet splitting for other medications, such as antihypertensives and antidepressants. It will also be useful to determine significant patient barriers to effective tablet splitting.

Conclusion

Splitting HMG tablets is an effective way to reduce outpatient drug costs, improving the efficiency in treatment of hypercholesterolemia. We found favorable humanistic-service outcomes (patient satisfaction and compliance) and no short-term negative effects on laboratory outcomes associated with tablet splitting of HMG drugs for outpatients at our institution.

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DISCLOSURES

No outside funding supported this study. Author Michael Gee served as principal author of the study and was primarily responsible for drafting of the manuscript. Study concept and design, analysis and interpretation of data, and critical revision of the manuscript was the work of Gee and authors Noelle K. Hasson, Terri Hahn, and Russell Ryono. All authors contributed statistical expertise. Administrative, technical, and/or material support was provided by Hasson, Hahn, and Ryono.

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Infection, Duration, And Complications Of Long Term Tunneled Hemodialysis Catheters (Lttc): A Retrospective Review

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Background: Long-term tunneled catheters (LTTC) for hemodialysis (HD) have been available for the past 15-20 years. They provide dialysis access for patients requiring hemodialysis, are used for patients awaiting arterial-venous (AV) fistulae to mature, and for other patients who have had peritoneal dialysis (PD) interrupted because of malfunctioning Tenchkoff catheters. But like any other central lines, these are associated with risks of infection, thrombosis and bleeding. This study will evaluate the duration, infectious and other complications associated with LTTC.

Methods: Between March 1995 and February 2000, patients at Shands Jacksonville with LTTC were identified. LTTC were placed under sterile procedure using ultrasound or fluoroscopically guided technique either by interventional radiologists or vascular surgeons.

Results: Types of LTTC included the Tesio, Perm Cath, and Ash Cath. A limited computer access to all patients having LTTC was utilized. A total of 50 patients were identified. Forty patients were suitable for study. There were 56 LTTC identified in these 40 patients. Of the 56 LTTC, 51 catheters were suitable for study (with known duration, date of placement and removal). Twenty-four study catheters (47%) were removed because of sepsis, bacteremia or fever with positive blood and/or positive catheter tip cultures. Organisms identified were methicillin sensitive Staphylococcus aureus (associated with 10 different catheters), coagulase negative Staphylococci (4), Pseudomonas acruginosa (4), methicillin resistant Staphylococcus aureus (3), Enterobacter cloacae (3), Acinctobacter baumannii (2), Enterococcus (2), E. coli (1) and Citrobacter (1). The most common complication was infection (24) (bacteremia and/or local wound infection). Endocarditis was observed in 2 patients. Other complications included thrombus formation (3), inadequate blood flow (3), fell or pulled out (3), and bleeding (1). Four patients died because of complications such as sepsis (2), endocarditis (1) and bleeding (1). The mean duration of catheters associated with infection was 99 ± 105 days (median: 49, range 11-371), while the mean duration of catheters not associated with infection was 76 ± 91 days (median: 50, range: 7-365).

Conclusion: Long term tunneled HD catheters serve a useful purpose for patients who are awaiting maturation of their permanent HD or PD access sites. The preliminary data suggests that LTTD are associated with a high rate of infection at this institution. The mean duration of catheters associated with infection was 99 days. Patients with these catheters should be followed and monitored carefully for signs and symptoms of infection and treated with aggressive antibiotics to avoid serious complications.

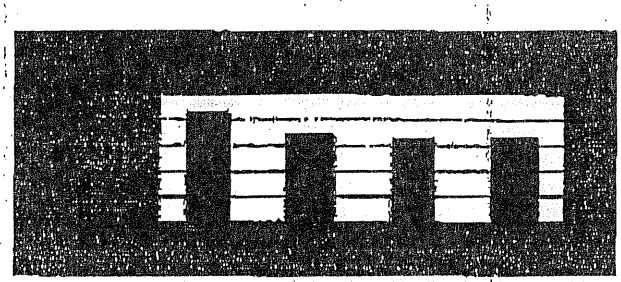
Evaluation Of Three Methods Of Administering Atorvastatin

P Schultz, Pharm.D., K Moran, Pharm.D., T Hogan, Pharm.D., K Malcolm, Pharm.D., M Zenni, M.D.; Resident, Department of Pharmacy

Background: Rising medication costs have led health care organizations to pursue alternatives to conventional medication dosing in hopes of decreasing drug expenditures. Patients are being asked to split tablets to receive the proper dose of medications at a lower cost. The atorvastatin 40 mg tablet is not scored, yet an increasing number of patients are splitting these tablets to receive a dose of 20 mg per day. In addition, alternate day dosing of atorvastatin 40 mg may provide similar therapeutic results at a lower cost to the patient and health care organization. The objective of this study is to compare three different methods of administering atorvastatin with respect to efficacy, cost savings and patient acceptance.

Methods: The study is a prospective, randomized, open label, crossover clinical trial. Consenting patients meeting criteria were randomized to one of three treatment arms (atorvastatin one whole 20 mg tablet daily, one-half 40 mg tablet daily or one whole 40 mg tablet every other day), with each treatment arm lasting six weeks. At the end of each treatment arm, labs were obtained and questionnaires administered before crossing over into the subsequent arm. Lipid values were compared to determine if there was a difference in therapeutic effect. Potential cost savings and patient acceptance were also evaluated.

Results: Twenty-nine patients were enrolled in the study. Data collection is ongoing. To date, no trends have been identified to indicate a therapeutic difference in the three dosing regimens being compared. Additionally, the majority of patients have not expressed difficulty in following the alternative dosing regimens. Based on the 29 patients enrolled, a cost savings of $976 per month, or $11,712 per year may be realized by utilizing one of the alternative regimens.



Conclusion/Discussion: Although larger studies are needed, tablet splitting and every other day dosing of atorvastatin appear to be a cost effective alternative to traditional once daily dosing.

Evaluation of Tablet-Splitting in Patients Taking Lisinopril for Hypertension

Joseph P. Rindone, PharmD

- *Objective:* To examine the efficacy of splitting lisinopril tablets in patients with hypertension and, secondarily, to assess patients' opinions regarding splitting lisinopril tablets.
- *Design:* Randomized, crossover clinical trial.
- *Setting:* Veterans Affairs medical center clinical pharmacy department.
- *Participants:* Twenty-nine veterans with hypertension taking stable doses of lisinopril.
- *Outcome measures:* Sitting blood pressure after 2 weeks of therapy. A 6-question survey was used to assess patients' opinions regarding the convenience of tablet-splitting and their willingness to split tablets.
- *Results:* No significant differences in systolic/diastolic blood pressures were noted between patients taking split versus full lisinopril tablets. Most patients were willing to split tablets if doing so would result in a cost savings.
- *Conclusion:* Using split lisinopril tablets does not result in a change in blood pressure in patients with stable hypertension. Most patients were willing to split tablets despite being inconvenienced.

Prescribing higher strength tablets that patients can split has been suggested as a feasible method of reducing acquisition costs of certain widely prescribed medications [1]. Whether this method should be used on a widespread basis remains controversial [2]. Some reports have described the success of splitting lovastatin and simvastatin in patients with hyperlipidemia [3,4], but few studies have examined the effectiveness and practicality of splitting other drugs, including blood pressure medicines. The purpose of this study was to examine the efficacy of splitting lisinopril tablets in patients with hypertension and, secondarily, to assess patients' opinions regarding splitting lisinopril tablets.

Methods

The study population consisted of outpatient veterans who received their primary care at the Veterans Affairs Medical Center in Prescott, Arizona, and were taking lisinopril for essential hypertension. Patients were selected at random from a computer-generated list of patients taking lisinopril, and their medical charts were reviewed. Patients with hypertension who lived locally and were taking a stable dose of lisinopril but had no diagnosis of congestive heart failure were sent a letter soliciting their participation in the study. Stable dose was defined as no change in dosing of lisinopril or any other hypertension medication within the previous 4 weeks.

Baseline blood pressure and heart rates were measured in patients who agreed to participate. Patients were then randomized in crossover fashion to either taking a full tablet or a split tablet once daily (Figure). Each treatment arm was 2 weeks in duration. Randomization was performed using a computer-generated list of random numbers. The dose of lisinopril used in the study matched the patients' prestudy dose whether they were taking full or split tablets (eg, patients in the split-tablet group who were taking a 10-mg dose before the study were given 20-mg pills and instructed to split them and take half the pill). All patients split tablets using a V-partition pill splitter. Patients were instructed to continue any other blood pressure medicine they had been taking before the study. Blood pressure was measured in the morning at the end of each treatment arm at approximately the same time of day for each patient. On days when blood pressure was measured, patients were instructed to withhold taking their morning dose of lisinopril until the measurement had been taken. Sitting blood pressure was measured using a mercury column sphygmomanometer in the same arm after the patient had been sitting for 5 minutes. The mean of 2 blood pressure readings taken 3 minutes apart was used. The last visit of the study occurred at 4 weeks; at this time all patients were asked to complete a survey with 6 questions regarding tablet-splitting.

The mean blood pressures for each treatment group were compared using a dependent *t* test. It was estimated that a sample size of 28 patients would have 80% power to detect a

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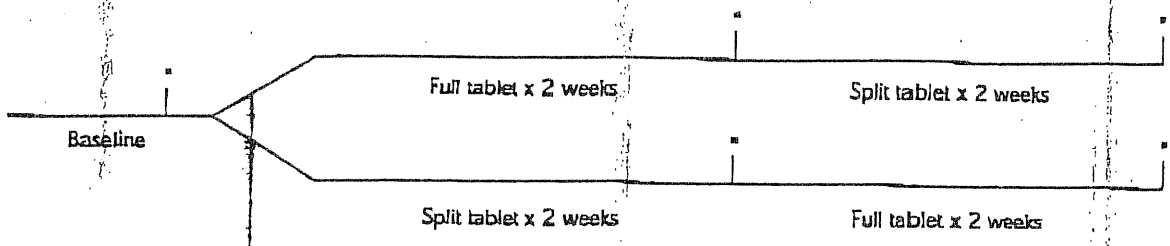

Figure. Randomization arms of lisinopril study. *Denotes when blood pressure was measured.

Table 1. Blood Pressure Measurements

	Mean Blood Pressure ± SD			
	At Baseline (All Patients)	After Split-Tablet Regimen	After Full-Tablet Regimen	*P* Value*
Systolic, mm Hg	133 ± 12	137 ± 12	136 ± 14	0.70
Diastolic, mm Hg	86 ± 8.5	87 ± 8.8	87 ± 9.3	0.70

SD=standard deviation.

*Difference between blood pressures in split-tablet and full-tablet patients.

5-mm Hg difference in diastolic blood pressure between treatment arms assuming a standard deviation of 8 and an alpha level of 0.05 [5].

An institutional review board approved this study, and informed consent was obtained from each patient.

Results

Twenty-nine patients completed the study. The mean age of patients was 71 ± 8.3 years. Twenty-six patients were men. The mean daily dose of lisinopril was 16 ± 36 mg. Twenty-three patients were on lisinopril monotherapy, 5 patients were taking 1 other antihypertensive drug, and 1 patient was taking 2 other antihypertensive drugs. Fifteen patients were randomized to the half-tablet/full-tablet schedule, and 14 patients were randomized to the full-tablet/half-tablet schedule.

No statistically significant differences in mean systolic or diastolic blood pressures were noted between treatment groups (Table 1). One patient (patient #30) complained of diarrhea while taking the full tablet and withdrew from the study. He was not included in the analysis.

Twenty-eight patients completed the questionnaire. There were mixed results regarding the convenience of splitting tablets and patients' ability to split tablets (Table 2). However, 89% and 97% of patients said they would be willing to split lisinopril tablets if there was a cost savings to themselves or to the facility, respectively.

Table 2. Survey Results

Item	Respondents, % (*n* = 28)
Splitting lisinopril tablets was bothersome to me:	
Most of the time	25
Some of the time	17
None of the time	58
I could split the lisinopril tablets down the middle:	
Most of the time	43
Some of the time	54
None of the time	3
When I split a lisinopril tablet, there were more than 2 pieces:	
Most of the time	3
Some of the time	54
None of the time	43
I drop lisinopril tablets when I'm splitting them:	
Most of the time	0
Some of the time	25
None of the time	75
I would be willing to split lisinopril tablets if there is a significant cost savings to the VA:	
Yes	97
No	3
I would be willing to split lisinopril tablets if I was paying for them myself and splitting tablets saved me money:	
Yes	89
No	11

Discussion

This study suggests that there is no meaningful difference in blood pressure when patients take split lisinopril tablets versus whole lisinopril tablets. This is the first study to use a pharmacodynamic endpoint to evaluate the effectiveness of splitting tablets. Other studies that addressed this topic either

surveyed patients on their willingness to split tablets, weighed split tablets, or measured compliance [6–9]. A study involving 105 veteran patients showed that overall compliance based on tablet count was the same whether patients split fosinopril tablets or used whole tablets [6]. In addition, this study found that the frequency of patients with compliance less than 80% was approximately the same between groups. The results of the present study support the finding that compliance is not impaired by having patients split lisinopril tablets.

An argument against tablet-splitting is that patients cannot split tablets accurately. A study supporting this argument involved healthy volunteers who split hydrochlorothiazide tablets and showed that more than 12% of the split tablets deviated from ideal weight by more than 20% [7]. A tablet splitter was not used in this study. Another brief report showed that although a V-partition pill splitter could split larger tablets accurately, accuracy was diminished with smaller tablets [8]. These findings suggest that drugs with narrow therapeutic indices should be taken as a whole tablet and not be split. However, this caveat may not apply to drugs with large therapeutic indices, such as lisinopril [10].

A second argument against splitting tablets is that it places an undue hardship on patients. Our survey results suggest that many veteran patients are inconvenienced by splitting tablets and at times have difficulty performing the task. However, when asked if they were willing to split lisinopril tablets in order to save money, virtually all of the patients were agreeable to doing so. Patients in 2 other studies responded similarly when asked about the monetary savings from splitting fosinopril or lovastatin tablets [6,9].

Potential flaws of the present study mandate that the findings be interpreted with some caution. This study involved a relatively limited number of patients, was not blinded, and had no washout period between treatments. Although the study was randomized, a possible carryover effect could have occurred. Also, because patients volunteered for the study, the cohort may reflect patients who are more motivated than the general population, limiting the study's findings to similarly motivated patients. Finally, it may be premature to apply these results to patients receiving lisinopril for other reasons, such as congestive heart failure.

This study suggests that splitting lisinopril tablets does not result in a significant change in blood pressure in patients with hypertension. Although some patients were inconvenienced by splitting tablets, the majority were agreeable to doing so if a cost savings was realized.

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and 7 can greatly affect study results. The problem can be solved by requesting that pharmacists write the number 7 with a horizontal bar through it, thus clearly distinguishing it from 1, or by having each value in a numerical field validated through a series of logical comparisons against a range of values. If these comparisons fail to resolve the discrepancy, then the value can be flagged for visual inspection.

Fax technology offers a reliable method of entering outcomes data into a computerized database. The reliability of the data collected in this study was very high and was influenced by the quality of the training the onsite pharmacists were given to show them how to complete the outcome-monitoring form, write legibly on the form before faxing it, fax the form correctly, and validate all the fax machines that would be used at each site.

It is very important to randomly select a percentage of patient charts at each site to check the reliability between (1) the charts and the data-collection forms and (2) the data-collection forms and the computer database.

Currently available data systems at the study sites did not provide the means for collecting the data necessary for this study. Since there was no computer-based system that was usable at all the types of sites where patients can be treated, the investigators created a unique, external data-collection process that could be used to capture data in an everyday, real-world treatment setting. Once the data are collected, this source of national information may be used again for further analyses or as a foundation for further data collection.

Conclusion. Fax technology that used optical mark and character recognition to scan data from an economic and outcomes study into a computer database had a reliability of at least 0.95 for each patient's complete set of data.

[a]Teleform, Cardiff Software, Vista, CA.
[b]Medical Outcomes Data Technologies, Laguna Beach, CA.

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Relationship between tablet splitting and compliance, drug acquisition cost, and patient acceptance

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As managed care pharmacy continues to grow and medication costs increase, pharmacy managers are continually looking for ways to reengineer distributive services to provide the most cost-effective care. In an effort to save money, the San Diego Veterans Affairs Healthcare System (SDVAHS) and other health systems have implemented tablet-splitting programs targeted at high-cost and widely prescribed medications. Despite this growing practice, published research examining the effects on compliance rates, patient acceptance, and actual cost savings is lacking. A recent computer-assisted literature search revealed only one study of tablet splitting that addressed patient compliance and acceptance.[1] In that study, patients taking lovastatin and using a tablet splitter were mailed a questionnaire to assess their impressions of tablet splitting. A majority of the patients found tablet splitters easy to use and reported that compliance was not hindered. However, compliance was subjectively evaluated through patients' responses to questions; actual tablet counts were not performed. Furthermore, actual cost savings (if any) were not determined.

We studied the relationship between tablet splitting and compliance, drug acquisition cost, and patient acceptance.

Methods. *Patient selection.* Patients with a prescription for 20-mg tablets of fosinopril sodium (Monopril, Bristol-Myers Squibb, Princeton, NJ), an angiotensin-

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Study patients were provided a tablet splitter (Health Care Logistics, Inc., Circleville, OH) by the San Diego Veterans Affairs Healthcare System.

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converting-enzyme inhibitor on the SDVAHS formulary, were identified from the computerized medication profiles from the pharmacy database for outpatients who were currently receiving medical care from SDVAHS. From this group, 1617 patients were identified on the basis of whether they split their 20-mg fosinopril tablets to obtain the prescribed dose: 971 patients split the tablets (and took one half tablet once daily), and 646 used whole tablets (and took one tablet once daily). Patients were then randomly chosen from each list to be contacted and evaluated for inclusion in the study. Random selection was achieved by assigning numbers from a randomization table to each patient. One hundred eighty eligible patients were then selected by using the last digit of their assigned numbers, starting with numbers ending in zero and continuing through the number nine.

Patients were included if they were 18 years of age or older and had had an active fosinopril prescription started at least three months but not more than three years before the study start date, October 1996. Patients had to receive the medication throughout the study period, October 1996 through May 1997. Patients were excluded from the study if they had taken another angiotensin-converting-enzyme inhibitor before starting fosinopril or had not refilled their fosinopril prescription in more than five months. Patients were then contacted by telephone and given specifics of the study. Those who wanted to participate were given an appointment and asked to bring all their fosinopril with them. Of the 105 patients who agreed to participate in the study, 47 split their fosinopril tablets and 58 did not.

The patients' appointments occurred during the study period. During an appointment, the investigator counted the fosinopril tablets remaining from the patient's last refill, and the patient answered a questionnaire about experience with tablet splitting, the presence of a caregiver (someone who gave the medications daily), any physical limitations (e.g., arthritis, poor vision, lost limb), and educational level. Educational level was assigned on the basis of the highest level of education completed (grammar school, high school or equivalent, college or university, graduate school, or doctorate). Patients who indicated that they had completed high school and had a vocational or technical school background were assigned the level of technical school. Other patient demographic data, such as age, copayment amount, number of active medications, and total number of daily doses of all medications, were available in the pharmacy database.

Compliance. Compliance assessment was based on tablet counting, refill history, and answers to a patient questionnaire. The tablet count was conducted by having the subject bring in any unused medication at the end of the evaluation period (last refill before the visit, plus any other unused tablets) and having it counted by the study examiners. Refill history was obtained from the hospital database. Compliance was assessed starting when the patient began fosinopril therapy and extending through the end of the study.

Compliance rate and percent compliance were calculated with the following equations:

Compliance rate = (total doses supplied – doses remaining)/(total days on medication)

Percent compliance = compliance rate × 100

A percent compliance of approximately 80% can be expected for medications taken once daily.[2,3] Therefore, the percentage of patients in each group with a percent compliance of <80% was also calculated.

Cost. Annual acquisition cost (AAC) was calculated with the following formula:

AAC = Compliance rate × tablet or half-tablet cost per day × 365 days per year

The difference in AAC per person in the two patient groups was calculated with both the 1997 federal supply schedule (FSS) and the average wholesale price (AWP). The FSS cost and the AWP of fosinopril did not vary by tablet strength.

Patient acceptance. Patients' satisfaction with tablet splitting and their impressions of its impact on medication taking were determined with a questionnaire adapted from the questionnaire of Carr-Lopez et al.[1,a]

Statistical analysis. To ensure a statistical power of 0.80 ($\beta = 0.20$) to detect a difference of 20% or more between the two patient groups with an α of 0.05 and an S.D. of 5.8, samples of 45 patients per group were needed. Descriptive analysis showed that the data for some of the variables did not have normal distributions. Therefore, nonparametric analyses were used. The Mann-Whitney *U* test was used to compare the interval and ordinal variables. Chi-square analysis with the Yates correction for continuity was used to compare all nominal variables.

Results. The two patient groups differed significantly with respect to age but not number of medications or doses taken per day, educational level, presence of a caregiver or physical limitations, or copayment requirement (Table 1).

Median percent compliance was 90.5% among the patients who did not split fosinopril tablets and 91.7% among the patients who did ($p = 0.67$, Mann-Whitney *U* test). The two groups also did not differ significantly in the percentage of patients with percent compliance of <80%: 30% of patients who did not split the tablets versus 29% of the patients who did.

The practice of splitting fosinopril 20-mg tablets resulted in a 50% reduction in median annual acquisition costs based on both FSS and AWP ($p < 0.001$, Mann-Whitney *U* test).

On the questionnaire, patients indicated that the tablet-splitting procedure was not detrimental to medication compliance. Specifically, 82% of the patients

agreed or strongly agreed that they had been adequately instructed on how to use the tablet splitter, 93% agreed or strongly agreed that tablet splitting did not change medication compliance, and 86% indicated that they thought the practice did not result in any more missed doses than taking whole-tablet doses (Table 2).

Discussion. Increased economic pressures facing the medical community have led to the implementation of various cost-saving measures, including having patients split tablets to obtain the prescribed dose. However, it is important to evaluate this potential cost-saving measure to ensure that a decreased acquisition cost by the health system or health plan does not correspond to a diminished clinical outcome. Therapeutic failures from medication noncompliance have also become a target of efforts to improve outcomes. It is well accepted that noncompliance can increase costs and decrease therapeutic effectiveness. Nevertheless, a lack of consensus on the best method of promoting compliance hampers efforts to minimize the impact of noncompliance on patient care and expense. Therefore, when implementing new cost-saving measures, such as tablet splitting, we should ensure that potential gains are not counteracted by negative effects in other areas.

There was no significant difference in compliance between patients who split fosinopril tablets and those who did not. To our knowledge, this is the first comparison of this kind. Cramer et al.,[4] using an electronic medication-event monitoring device, reported a compliance rate of 87% with once-daily, self-administered medications. We attribute the overall higher compliance rate in our study to the use of the pill-count method. As Pullar et al.[2] independently concluded, the pill-count method overestimates compliance.

The questionnaire results reinforce the conclusions drawn from our pill-count data and are congruent with those reported by Carr-Lopez et al.[1] The strong positive experiences expressed by the tablet-splitting patients, the consistency of these results with previous findings, and the similar compliance rates between the two groups of patients suggest that tablet splitting has little negative impact on compliance or patient acceptance.

A 50% decrease in estimated annual acquisition cost was found, mainly because of the advantageous pricing structure of fosinopril (tablets may be purchased at the same price regardless of strength) and the negligible cost to SDVAHS for the pill cutters ($1.05 per unit). If our patients had to bear more of the cost for their medications, as with patients who have medical insurance without a drug benefit, the 50% savings from splitting fosinopril would, we believe, further improve patient acceptance of tablet splitting. Nonetheless, a reduction in acquisition cost of this magnitude may not be achieved with all tablet-splitting applications. Factors such as tablet pricing and compliance barriers (e.g., large tablets, difficulty of

Table 1.
Demographics of Study Patients

Characteristic	Patients Who Took Whole Tablets (n = 58)	Patients Who Split Tablets (n = 47)
Median age, yr	61	65[a]
Male sex, %	100	100
Median no. medications taken daily	6	6
Median no. doses taken daily	8	8
Median educational level	Technical school	High school
Presence of a caregiver, no. (%)	9 (16)	2 (4)
Presence of physical limitations, no. (%)	0 (0)	2 (4)
Paying copayment, no. (%)	45 (78)	36 (77)

[a]Significantly different from value for other group, p = 0.034 (Mann-Whitney U test).

Table 2.
Patients' Acceptance of Splitting Tablets To Obtain Prescribed Dose

Statement	n	Answer
I was given inadequate instructions on how to use the tablet splitter.	55	Strongly agree, 47%; agree, 35%; neutral, 0%; disagree, 2%; strongly disagree, 16%
Tablet splitting had no effect on my willingness to take my medication.	56	Strongly agree, 50%; agree, 43%; neutral, 4%; disagree, 4%; strongly disagree, 0%
Compared to my other medications that I do not cut in half, I miss _____ doses when I have to cut the tablets.	57	Many more, 2%; a few more, 12%; the same number, 2%; a few less, 5%; no, 79%
I consider the extra time needed for tablet splitting to be negligible.	57	Strongly agree, 47%; agree, 39%; neutral, 9%; disagree, 2%; strongly disagree, 4%
If I had to pay the full expense of my medication, I would split tablets if it could save me 25–55% of my medication cost.	57	Strongly agree, 60%; agree, 33%; neutral, 2%; disagree, 2%; strongly disagree, 4%
I may miss a dose because I do not want to, or have not, split my tablets.	57	Strongly agree, 4%; agree, 2%; neutral, 4%; disagree, 30%; strongly disagree, 61%
How many times in the last month did you throw a tablet away because of a problem related to tablet splitting?	57	0–1 time, 91%; 2–10 times, 9%; 11–20 times, 0%; over 20 times, 0%; I did not take my medication, 0%

utting) can dramatically alter cost savings and patient acceptance.

Specific limitations of this study provide the opportunity for additional research to further assess the impact of tablet splitting on compliance, pharmacoeconomics, and patient acceptance. We chose patients using half of a 20-mg tablet or a whole 20-mg tablet because there were a relatively high number of patients receiving 10 and 20 mg of fosinopril per day. This helped ensure a sufficiently large sample. We wanted to minimize the number of patients who could be lost to dose-related adverse effects by selecting patients taking no more than 20 mg daily. It would have been better, from a methodological standpoint, to compare patients taking equivalent dosages (e.g., half of a 20-mg tablet versus a whole 10-mg tablet); cost analyses should not have been affected since the cost of fosinopril was similar for all tablet sizes.

The two major limitations of this study derive from time, study-design, and financial constraints. Because a physiological endpoint, such as blood pressure, was absent from the study, the impact of splitting tablets on physiological outcomes could not be determined. Although this study's use of pill counting to determine compliance may be considered less than optimal, it continues to be widely used in clinical trials.[2,5-8] If not for the cost, however, our preference would have been to objectively measure compliance with an electronic monitoring device. Measuring physiological impact may determine if splitting tablets results in a decreased physiological response secondary to medication waste. Two studies have quantified drug waste when tablets are split, but neither study attempted to determine whether the loss resulted in a clinically important reduction in physiological effect.[8,9] Monitoring blood drug levels (which would not provide useful information for our study) and providing patients with devices that measure compliance have also been reported to be imprecise means of quantifying efficacy in terms of compliance.[2,4,5]

This study of an angiotensin-converting-enzyme inhibitor demonstrates potential benefits of tablet splitting. Caution and good clinical judgment should be used before extrapolating these findings to tablet-splitting programs involving other medications.

Conclusion. Patients' use of a tablet splitter on oval, unscored tablets decreased a health system's acquisition costs for the drug without affecting patient compliance, compared with use of whole tablets. Tablet splitting was well accepted by the patients.

[a]The questionnaire was adapted with permission (Carr-Lopez SM, personal communication, 1996 Sep 10).

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The Outcome of Very Low Dosages of Simvastatin in Patients with Hypercholesterolemia

Joseph P. Rindone, Pharm.D.

A retrospective study evaluated the success of dosages of simvastatin lower than the 10–20 mg/day recommended by the manufacturer in patients with hypercholesterolemia. Records of 95 patients enrolled in a pharmacist-managed lipid clinic receiving stable dosages of simvastatin were reviewed. Data collected were demographics, number of simvastatin refills, dosage distribution, baseline and posttreatment lipid profiles, and proportion of patients with low-density lipoprotein (LDL) levels below target as recommended by the National Cholesterol and Education Program. Dosages for 62% of patients were less than 20 mg/day. Percentages of patients at goal LDL were 98%, 89%, and 83% for patients taking 2.5, 5, and 10 mg/day, respectively. Patients taking 40 mg/day were least likely to be below the goal. There was an even distribution of patients taking each dosage. No statistical difference in compliance was noted among dosages based on prescription refills. Most patients taking less than the recommended initial dosage of the agent had satisfactory lipid control.
(Pharmacotherapy 1999;19(4):399–403)

The manufacturer of simvastatin recently increased the usual recommended starting dosage from 10 to 20 mg/day.[1] Although a daily dose of 20 mg is highly effective in lowering cholesterol, smaller doses are also effective and may be adequate for many patients with hypercholesterolemia.[2] In addition, smaller doses reduce the risk of dose-related side effects and significantly lower pharmacy costs for both patients and third party payers.

At this facility's lipid clinic, the starting dosage of simvastatin is considerably lower than that recommended by the manufacturer and titrated based on response. Since few data describe the effectiveness of this strategy in a nonresearch setting, we reviewed patients enrolled in the clinic who were taking the drug to assess the outcome, with emphasis on dosages below 20 mg/day.

Methods

A clinical pharmacist in consultation with nutrition and medicine services manages the lipid clinic. All patients are referred to the clinic from primary care providers. Approximately 200 patients are currently enrolled in the clinic.

Patients receiving simvastatin who were followed at the lipid clinic were reviewed retrospectively. To be eligible for review, patients had to be taking simvastatin for a minimum of 8 weeks and considered to have stable lipid control. The dosage of simvastatin was adjusted to low-density lipoprotein (LDL) levels as recommended by the National Cholesterol and Education Program (NCEP).[3] The usual starting dosage was 2.5 mg/day at bedtime and was increased according to response to a maximum of 40 mg/day. Patients were instructed to cut tablets in half with a V-partition pill splitter. Those who were unable to do this and those receiving 40 mg/day took full tablets. Patients returned to the clinic within 8–12 weeks after starting therapy or after a dosage change to have blood drawn for lipid profile (total cholesterol, triglycerides, LDL, high-density lipoprotein) and liver profile. At each visit the clinic provider assessed the patient's lipid profile with specific attention to target LDL level.

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Table 1. Demographics and Compliance of Patients Who Were at the Final Dosage of Simvastatin

Daily Dose (mg)	No. of Patients	Mean ± SD Age (yrs)	Compliance[a] (%)	No. with < 2 Cardiac Risk Factors	No. with ≥ 2 Cardiac Risk Factors	No. with Coronary Disease
2.5	20	64 ± 12	93	6	6	8
5	20	66 ± 6	90	4	8	8
10	18	66 ± 9	93	3	8	7
20	18	67 ± 9	95	2	2	14
40	19	62 ± 9	99	0	4	15

[a]See text for definition of compliance.

Dosages were increased only in patients not at the LDL goal who appeared to be compliant with both diet and drug therapy and who tolerated the agent. Dosages were generally not increased if patients were within 5 mg/dl of the LDL target. Reductions were was attempted in those who had side effects to simvastatin or whose LDL levels were markedly below target. Compliance with therapy was assessed by dividing the number of 30-day prescription refills by the number of months of therapy up to a maximum of 6 months.

Data collected included demographics, daily dose of simvastatin, number of refills, cardiac risk factors based on NCEP guidelines, and lipid profiles before and after simvastatin therapy. Baseline lipid profiles were the most current ones while not receiving lipid-lowering therapy. Posttreatment lipid profiles were the most recent after a minimum of 8 weeks of simvastatin treatment. Low-density lipoprotein levels were calculated by the laboratory using the Friedewald formula in patients in whom triglyceride levels were below 400 mg/dl.[4] Lipid profiles were considered fasting since all patients were routinely instructed to fast 12 hours before laboratory appointments for these tests.

One-way analysis of variance was used when comparing means (patient age, LDL levels), and χ^2 or Fisher's exact test for proportional data (SigmaStat, San Rafael, CA).

Results

Ninety-five patients met eligibility requirements (mean age 65 ± 9 yrs; 92 men, 3 women). Patients not meeting requirements were receiving alternative treatment or were undergoing simvastatin dosage titration due to unsatisfactory lipid control. There was no statistical difference in patient age among dosages. Fifteen patients had fewer than two risk factors, 28 had two or more risk factors, and 52 had coronary artery disease. Most patients who received high dosages had coronary disease (Table 1). For 29 patients the starting dosage of simvastatin prescribed in the clinic was 2.5 mg/day. Higher dosages were started by a primary care provider before these patients were referred to the clinic. All patients cut the tablets in half, except one who was receiving 5 mg/day and all those receiving 40 mg.

Sixty-two percent of patients had dosages less than 20 mg/day (Figure 1). There was even distribution of patients receiving each dose in the entire cohort (p=0.98). No statistical difference in compliance was noted at any dosage. Reduction in LDL per dosage was analyzed by separating instances where dosage escalation was necessary and when the final dosage was attained (Tables 2 and 3). A smaller reduction in LDL was evident at each dosage (2.5–20 mg/day) in patients in whom the dosage was increased, compared with final dosages (p<0.05, 2.5 and 20 mg/day). The largest percentage of patients at goal LDL levels were those receiving 2.5 mg/day (Table 4) and the lowest with those taking 40 mg (p=0.04, 2.5 vs 40 mg). As the dosage increased, fewer patients were at goal LDL.

The most common reasons for not increasing the dosage in patients above LDL goal were

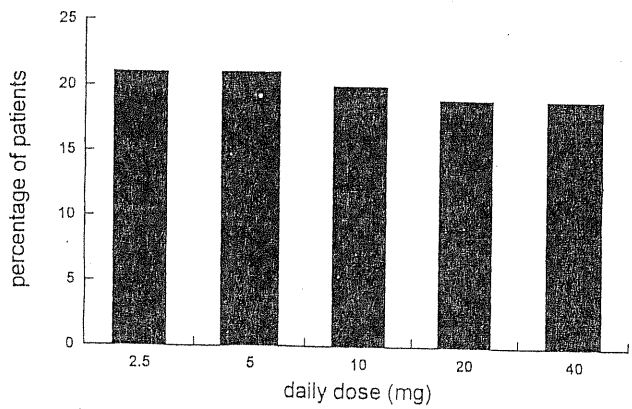

Figure 1. Distribution of final simvastatin dosages.

Table 2. Lipid Values before and after Simvastatin in Patients Who Were at the Final Dosage

Daily Dose (mg)	No. of Patients	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	Change in LDL (%)
2.5 baseline	20	253 ± 33	243 ± 87	36 ± 10	167 ± 25	33
After		195 ± 25	214 ± 98	40 ± 8	111 ± 28	
5 baseline	20	263 ± 32	241 ± 91	37 ± 10	180 ± 29	40
After		191 ± 29	239 ± 139	41 ± 12	107 ± 19	
10 baseline	18	265 ± 36	236 ± 86	39 ± 9	181 ± 26	37
After		197 ± 29	212 ± 75	43 ± 8	114 ± 24	
20 baseline	18	255 ± 36	303 ± 135	35 ± 12	155 ± 15	36
After		188 ± 28	247 ± 86	39 ± 10	99 ± 24	
40 baseline	19	272 ± 43	281 ± 151	40 ± 14	195 ± 56	45
After		192 ± 25	263 ± 153	38 ± 8	106 ± 27	

Data are expressed as mean ± SD.

Table 3. Lipid Values before and after Simvastatin in Patients Who Had a Subsequent Dosage Increase

Daily Dose (mg)	No. of Patients	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	Change in LDL (%)
2.5 baseline	9	254 ± 32	200 ± 88	41 ± 12	173 ± 29	17
After		232 ± 29	195 ± 77	49 ± 10	143 ± 22	
5 baseline	4	255 ± 34	300 ± 120	41 ± 10	150 ± 8	22
After		224 ± 39	370 ± 230	38 ± 5	116 ± 11	
10 baseline	10	253 ± 18	299 ± 117	35 ± 12	155 ± 10	14
After		216 ± 28	237 ± 117	40 ± 7	132 ± 28	
20 baseline	13	277 ± 53	261 ± 129	43 ± 16	189 ± 68	21
After		236 ± 27	241 ± 122	42 ± 8	148 ± 29	

Data are expressed as mean ± SD.

Table 4. Number of Patients at Target LDL Who Were at the Final Dosage

Daily Dose (mg)	< 2 Risk Factors	≥ 2 Risk Factors	Coronary Disease	Total (%)
2.5	6/6[a]	5/4	8/8	95[b]
5	4/4	7/7	7/5	89[c]
10	3/3	7/5	8/7	83
20	2/2	2/2	14/8	66
40	0	4/3	13/8	65[c]

[a]Number of total patients/number at goal.
[b]One patient taking this dose did not have LDL estimated.
[c]Two patients taking this dose did not have LDL estimated.

noncompliance with diet, and maximum dosage already prescribed (Table 5). Other reasons were side effects at higher dosages and LDL levels that were within 5 mg/dl of the target.

Discussion

In approximately 60% of patients hyperlipidemia was controlled with simvastatin dosages less than 20 mg/day. This success in maintaining lower dosages could be attributed in part to selecting patients who were considerably more responsive to that agent as opposed to those who were not. This is evident since patients who required a dosage escalation had less reduction in LDL than those receiving final dosages.

Statin responsiveness was observed by others. One study detailed LDL lowering of five statin drugs at various dosages as a mean percentage versus baseline.[5] The standard deviation for these means ranged from 7–14%, suggesting that some patients were significantly more responsive to statins than the average patient. Another study reported that simvastatin 5 mg/day lowered LDL by a mean of 23% in patients with primary hypercholesterolemia.[6] When the magnitude of LDL reduction at that dosage was analyzed separately, 12% of patients had an LDL reduction

Table 5. Reasons for Not Increasing Simvastatin Dosages in Patients Not at LDL Goal

Reason	Daily Dose				
	2.5 mg	5 mg	10 mg	20 mg	40 mg
Dietary noncompliance	1	—	3	2	—
Higher dosages not tolerated	—	1	—	3	—
LDL within 5 mg/dl of goal	—	1	—	1	—
Maximum dosage[a]	—	—	—	—	6

[a]The maximum dosage at the time of the study was 40 mg/day.

of 40% or greater and 54% had reductions ranging from 20–39%. This may be the type of patient that we treat when we successfully prescribe lower dosages of simvastatin. Contrary to this, patients who require higher dosages may be more resistant to the agent or have lower target LDL levels in relation to baseline.

Starting therapy with high dosages of simvastatin has a potential advantage of producing lower LDL levels than smaller dosages. Whether this is an advantage in increasing protection against vascular events is unclear. One study has suggested that a 1% decrease in total cholesterol leads to a 2% decrease in coronary risk.[7] Further analysis suggested that a lower LDL level confers additional cardiovascular protection in patients with coronary artery disease, although the beneficial effect wanes as the LDL is lower.[8] Few prospective dose-response studies with lipid lowering drugs support these findings. In one study, higher dosages of lovastatin were superior to lower dosages in promoting graft patency in patients who underwent coronary bypass surgery.[9]

Applying these findings in the framework of primary and secondary prevention is difficult. In the setting of primary prevention, a trial with pravastatin concluded that a 24% reduction in LDL was optimal in reducing the risk of cardiac events, and additional lowering was of no benefit.[10] It is interesting that a mean 24% reduction in LDL was described with simvastatin 5 mg/day.[11]

Another argument for starting at higher dosages of simvastatin is that dosage titration may be avoided, which would reduce clinic visits and laboratory monitoring. This may be particularly true when the pretreatment LDL is significantly elevated and/or the target goal is 100 mg/dl. This strategy ignores the possibly that a significant cost may be incurred by many patients who could be controlled with lower dosages, especially those who have a mild to moderate elevation in LDL in relation to target levels. Our results suggest that over 60% of patients can probably achieve adequate lipid control with dosages below 20 mg/day.

Using average wholesale prices, the monthly cost of simvastatin 20 mg is approximately $108, compared with $62 for 10 mg, $53 for 5 mg, and $26 for 2.5 mg (1/2 a 5-mg tablet). Taking half-tablets for 5- and 10-mg doses would lead to additional savings. Price differences between doses may be less in managed care plans and government institutions since contract pricing may come into play. Even so, these differences may offset the cost of extra clinic visits and laboratory since the duration of therapy for most patients is several years to life.

All patients in the lipid clinic are instructed to split simvastatin tablets in half to reduce pharmacy costs. A potential disadvantage is that this may be a hardship and possibly lead to noncompliance. Using a commercial pill splitter is a simple way of dividing unscored tablets relatively accurately.[12] Absolute accuracy is probably not essential, since the drug is considered to have a broad therapeutic window.[13] Simvastatin tablets are not round, are rather small, and are not approved for splitting by the manufacturer. However, when patients used a V-partition splitter (usual retail price $3) and were instructed on how and why to cut tablets, most were willing and able to perform this simple task. They did it successfully when fluvastatin was changed to simvastatin at a dosing a ratio of 8:1 and patients split tablets.[14]

Conclusion

Most patients followed in a pharmacy-managed lipid clinic had adequate lipid control with simvastatin dosages lower than that recommended by the manufacturer.

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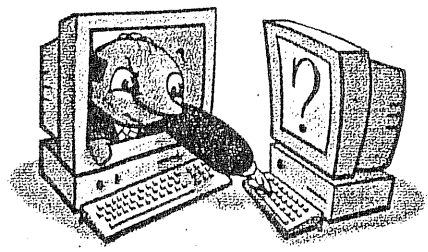

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COMPILED BY JANET KALBFLEISCH

research suggests eight times more members prefer outpatient benefits. "Hospitalization is expensive. If we had to offer both, some people would drop their insurance."

That argument doesn't wash with advocates. Both inpatient and outpatient care, they believe, should be part of any basic package. "Missing either is totally indefensible for a health plan," says Rusty Selix, executive director of the California Mental Health Association, Sacramento. "It's like cutting off your right arm to fix your left leg."

Hospitals aren't happy, either. "You always have a certain percentage who will need hospitalization," says Pat Ryan, vice-president for behavioral health at the California Healthcare Association, Sacramento. "That's why you have health insurance."

Consumer advocates say they're hearing more stories about plans closing crisis clinics or refusing to pay for hospitalization. Ryan says several insurers have dropped inpatient psychiatric benefits altogether.

Blue Shield counters that it's simply being careful with limited resources. Be July 1, the plan didn't cover outpatient n tal heath at all. "We chose to offer outpat and drug services because more pe access those," Perry says. For patients are suicidal or acutely psychotic, the allows a five-day emergency hospital s

The Blue Shield move is helping f up support in California for a parity requiring coverage of mental illness at same level as physical illness. The fed parity law is considered weak by many, the California Legislature is poised strengthen protections—even mandat a mental health benefit in all health pl

Mental health advocates argue tha cheaper to get early treatment instead waiting for a crisis to happen. "Intervent saves costs down the line," says Ran Hagar, who follows legislative issues for Sacramento-based California Alliance the Mentally Ill. "When somebody doe get inpatient care, they just get wor

—JAN GREENE ●

DRUG COSTS

Double Your Measure

Antidepressants like Prozac, Paxil, and Zoloft account for a bigger-than-ever share of the pharmacy benefit dollar, but Washington state's Medicaid program and two Nevada HMOs aren't worrying: They're cutting the cost of depression-fighting drugs in half—literally.

Medicaid officials are asking doctors to prescribe double doses of Zoloft and Paxil, as well as antidepressants Effexor and Serzone. Pharmacists then split the pills in half so patients can take the proper dosage.

The tactic is a big money-saver. T average wholesale price for a hundred 5 mg. tablets of Zoloft, for example, is abc $227, while a hundred 100-mg. tablets c just $6 more. The savings after splittir about $220.

Washington state's 15-month-o program is voluntary; pharmacists alwa ask whether the customer would mind ta ing a pill that's been cut along the score lir Says Medicaid pharmacy research specia ist Siri Childs, "We don't force the patient

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take a split pill." If the program had been in effect in 1997, Childs says, splitting just Effexor and Serzone pills that year would have saved more than $350,000.

Health Plan of Nevada, headquartered in Las Vegas, has enrolled 3,000 of its 185,000 members in a pill-splitting program involving Zoloft, the antidepressant Celexa, and Lipitor, a cholesterol-lowering drug. The patient, not the pharmacist, splits the pills, using a tablet-cutting device supplied by the plan. All patients on these drugs must take part in the program unless their doctor is against it, says spokeswoman Jenny DesVaux Oakes. "We're committed to having a prescription drug benefit, and the pill-splitting program helps us do this."

NOT TO SPLIT: Pill splitting can lead to big savings, but some fear patient harm.

Plan officials won't estimate total savings, since it's unclear how long patients will be on a drug regimen. Still, it's not chump change, says Oakes. The medications cost an average $60 to $75 a month per patient, she says. "If you halve that, you can figure out how much the savings are."

Another Nevada HMO, Reno-based Hometown Health Plan, inaugurated a Zoloft-splitting program more than two years ago. In 1998, some 3,700 claims for the 100-mg. tablet were filed, compared with 445 for the 50-mg. version. The Zoloft program has been in place for more than two years, but some patients still receive 50-mg. tablets because their doctors fear they can't divide the pills accurately. Hometown

John Eudes

John Eudes might seem like an improbable Internet entrepreneur. He isn't a thirtysomething from the West Coast, and he spent many years in hospital senior management—a hectic field, to be sure, but a far cry from Silicon Valley. But Eudes' career has had its share of metamorphoses. Before becoming a health care marketing exec, he worked as both an accountant and a college professor. Today, he's on the road half the year as president of Greystone.net, an Atlanta firm that helps health systems design their Web sites. Understandably, Eudes has a hobby that's close to home and low tech: yard work. "People stop to ask me what lawn service I work for," says Eudes. "Then I have to tell them I live here." —TERESE HUDSON

Best advice I received
While working as an accountant, I felt stifled. My dad said if I stayed creative and persisted in accounting, I'd probably wind up in jail.

Biggest risk
Going into health care. My wife is a nurse, and I kept seeing opportunities to apply marketing principles to health care. Twenty-five years ago, most hospital managers weren't thinking in those terms.

Advice to others
Strategy matters. Technology often distracts us. Too many people created Web sites and then said, "What are we trying to accomplish?"

Strangest habit
I watch TV for the commercials and read during the programs. The ads are more creative, and I like to figure out what each commercial is trying to do and whether it's effective.

Contact John Eudes at jeudes@aol.com

PHOTOGRAPH BY STAN KAADY

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has ruled out certain other prescription drugs, plan officials say, because the pills lacked a score mark.

Pill-splitting may stretch the health care dollar, but not everyone loves the idea. Rabindra Patnaik, a pharmacologist with the FDA's Office of Generic Drugs, Rockville, Md., says unscored pills can't be accurately halved, so the drug content wouldn't be the same for each portion.

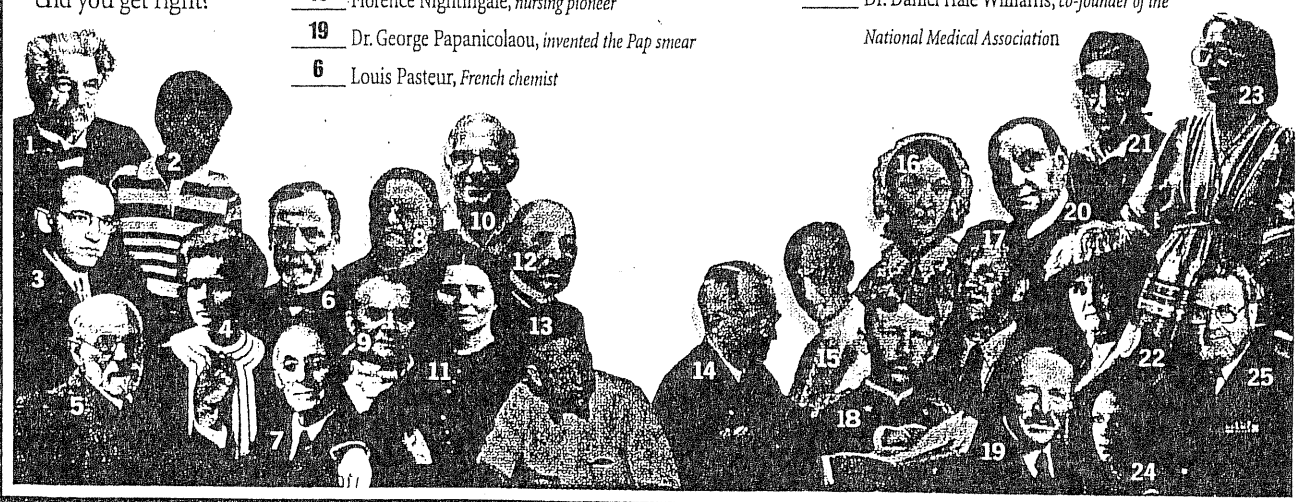
That's also the case with sustained-release pills or ones with enteric coatings, says Charles Myers, a vice-president of the American Society of Health-System Pharmacists, Bethesda, Md. "A patient ma receive an insufficient concentration of th medicine." Also, patients who receive spl pills may think they can take fewer or small er doses of other drugs. That, Myers says could be just as harmful as a medicatio error. —CHRISTINA ERDMANN ●

CONTEST ANSWERS

25 Who Shaped Health Care

In the May 1999 issue, *H&HN* asked readers to name these 25 faces from the past who have changed the shape of health care. Ten lucky winners received a free copy of *100 Faces of Health Care*, published by AHA Press. Here's a list of the winning answers. How many did you get right?

22 Jane Addams, *social worker, founded Hull House*
11 Clara Barton, *founder of the American Red Cross*
9 Barney Clark, *artificial heart recipient*
4 Marie Curie, *Nobel Prize for discovering radioactivity*
21 Michael DeBakey, *heart surgery pioneer*
7 Abraham Flexner, *medical school reformer*
5 Sigmund Freud, *Austrian neurologist*
17 Henry J. Kaiser, *industrialist and health care philanthropist*
13 Alfred Kinsey, *sexologist*
25 Dr. C. Everett Koop, *health activist, former surgeon general*
23 Elizabeth Kübler-Ross, *psychiatrist,* On Death and Dying
15 Dr. Peter B. Medawar, *Nobel Prize for transplant immunology*
16 Florence Nightingale, *nursing pioneer*
19 Dr. George Papanicolaou, *invented the Pap smear*
6 Louis Pasteur, *French chemist*
24 Karen Ann Quinlan, *coma victim whose parents became right-to-die activists*
18 Maj. Walter Reed, *found cure for yellow fever*
3 Dr. Jonas Salk, *co-discovered the polio vaccine*
1 Dr. Albert Schweitzer, *missionary who treated leprosy and sleeping sickness*
10 Dr. Benjamin Spock, *pediatrician*
8 Dr. Etienne Tarnier, *inventor of human incubators*
14 Harry S Truman, *president, national insurance champ*
2 Ryan White, *AIDS activist*
20 Harvey Washington Wiley, *championed regulation of food and drug industries*
12 Dr. Daniel Hale Williams, *co-founder of the National Medical Association*



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1999 Facts and Comparisons

FROM YOUR NEWSLETTER

Sertraline Tablet Splitting Program

Judilynn Bult, PharmD, BCPS, Gordon Schiff, MD,** and Mary Wisniewski, RN†*

Hospital Pharmacy *welcomes contributions to this column. Articles originally published in pharmacy department newsletters are reprinted here. Material is selected because of its educational value to pharmacists or because it demonstrates the type of information of interest to newsletter readers. If you wish to have your newsletter material considered for publication in this column, mail a copy—along with a computer disk containing the document—to Neil M. Davis, Editor-in-Chief,* Hospital Pharmacy, *1143 Wright Drive, Huntingdon Valley, PA 19006-2721.*

Cook County Hospital's (CCH's) quality assurance staff, pharmacy staff, and medical staff have been working together as participants in the Institute for Healthcare Improvement (IHI) Breakthrough Series on Improving Prescribing Practice (IPP). We applied the improvement model learned from IHI to hold down costs for an expensive but important outpatient class of medications—SSRIs (selective serotonin reuptake inhibitors).

We learned from another, collaborative hospital that we could save considerable money by breaking sertraline (*Zoloft*) 100 mg tablets in half. Since the 50 mg tablets cost approximately the same as the 100 mg tables (CCH price is $1.42 vs $1.46/tablet), patients would in effect receive two tablets for the price of one, if the 100 mg tablets were broken. Using this technique, we were able to achieve substantial cost savings.

An educational brochure for patients was prepared (see Figures 1a and 1b). We consulted with the Department of Psychiatry and the Drug and Formulary Committee (CCH equivalent of a pharmacy and therapeutics committee) before the Sertraline Tablet Splitting Program was launched on June 15, 1998.

What follows is a summary of our project, presented in the IHI format: Aim, Method, Rationale, Interventions, Data, and Conclusions. As the summary conveys, an annual savings of more than $200,000 is now being realized. We found that a simple but valuable maneuver can save money that can be redirected toward improving patient services.

AIM

- To decrease dollars spent on sertraline at Cook County Hospital

Savings of $100,000 to $120,000 per year with minimal expense were anticipated.

METHOD

Beginning on June 15, 1998, prescriptions for sertraline 50 mg were written and dispensed as *one-half* of a sertraline 100 mg tablet.

RATIONALE

The cost to CCH for sertraline is:

- $1.42 per 50 mg tablet
- $1.46 per 100 mg tablet
- $0.73 per each half of a 100 mg tablet

INTERVENTIONS

1. The primary physicians, psychiatric staff, and internal medicine staff were educated about the program and encouraged to write prescriptions for sertraline 50 mg once daily as "sertraline 100 mg 1/2 tablet once daily."
2. The pharmacist, regardless of the directions, will dispense the 100 mg tablet when the 50 mg dose is ordered per policy.
3. The pharmacist will instruct the patient to split the 100 mg tablet, resulting in a 50 mg dose. An educational brochure will be given to the patient, instructing/re-enforcing this message and explaining the reason for the substitution.
4. The pharmacy will dispense the appropriate supply as indicated on the prescription or according

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- Sertraline (Zoloft®) is used to treat mental depression
- **Possible Side Effects**: deceased appetite or weight loss; decreased sexual drive or ability; diarrhea; drowsiness; dryness of mouth; headache; nausea; stomach or abdominal, gas, or pain; tiredness or weakness; tremor; trouble in sleeping.
- **Precautions:** This medication could possibly add the the effects of alcohol and other medicines such as antihistamine or medicines for hay fever, other allergies, or colds; sedatives, tranquilizers, or sleeping medicine; prescription pain medicine or narcotics; barbiturates; medicine for seizures; muscle relaxants; or anesthetics; including some dental anesthetics. *Check with you doctor before taking any of the above while you are using this medicine.*
- It is important for you doctor and pharmacist to know if you are also taking digitoxin, warfarin or a monoamine oxidase inhibitor
- **You may have to take sertraline for 4 weeks or longer before you begin to feel better.**

Adapted from *1993 The United States Pharmacopeial Convention, Inc* ©

COOK COUNTY HOSPITAL
Department of Pharmacy
1835 West Harrison Street
Chicago, IL 60612-9985

COOK COUNTY HOSPITAL

IMPORTANT INFORMATION ABOUT YOUR SERTRALINE (ZOLOFT®) PRESCRIPTION

FROM YOUR PHARMACIST

FIGURE 1a. Patient education brochure (sides 1 and 4)

SERTRALINE, ALSO CALLED ZOLOFT

Your doctor wants you to take sertraline 50mg everyday. You will be getting sertraline 100mg tablets which are yellow. Please break the yellow tablets in half. One-half of a yellow tablet is equal to one 50mg tablet which is blue.

We are asking you to break the tablets in half to help us save money. The money we save on this medication can be used to take better care of you in other ways.

HOW TO BREAK A TABLET IN HALF

1 Find the line on the middle of the yellow tablet

2 Hold the tablet with both hands between your first finger and thumb.

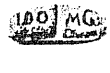
3 Place your thumbs on either side of the line.

4 Snap the tablet away from you. It should break easily.

5 If you are unable to break the tablets, your doctor may request the 50mg tablets.

6 1/2 yellow tablet = 50mg

= 50mg



= 100mg


= 50mg + 50mg

CCH DEPARTMENT OF PHARMACY
(312) 633-7897

FIGURE 1b. Patient education brochure (sides 2 and 3)

TABLE 1

Results of Sertraline Tablet Splitting Program

	No. Rx's	*No. Patients*	*Total No. Tablets*	*Cost/Tablet ($)*	*Total Cost ($)*
April 1998					
50 mg	791 (81%)	524 (74%)	26,606	1.42	37,780
100 mg	185 (19%)	180 (26%)	12,434	1.46	18,154
Total	976	704	39,404	-	55,934
July 1998					
50 mg	542 (55%)	250 (37%)	12,225	1.42	17,360
100 mg	442 (45%)	425 (63%)	20,497	1.46	29,926
Total	984	675	32,752	-	47,286
September 1998					
50 mg	505 (50%)	244 (24%)	8,219	1.42	11,671
100 mg	503 (50%)	493 (76%)	23,329	1.46	34,060
Total	1008	981	31,548	-	45,731
January 1999					
50 mg	77 (10%)	71 (12%)	3,436	1.42	4,879
100 mg	724 (90%)	541 (88%)	19,624	1.46	28,651
Total	801	612	23,060	-	33,530

to pharmacy policy.

5. If any patient, for any reason (eg, significant psychiatric contraindication, physical disability) is not able to tolerate tablet splitting, the physician may so designate. The pharmacy will then dispense the 50 mg tablet.
6. The goals of the program were published internally in the pharmacy newsletter and distributed to all medical staff.

DATA

See Table 1.

CONCLUSIONS

The sertraline tablet splitting program began on June 15, 1998. After comparing data from April 1998 (before the implementation), July 1998 (after the implementation) September 1998 (after reporting results to the pharmacy staff), and January 1999 (after additional reinforcement efforts), the following conclusions can be made:

1. The number of sertraline prescriptions dispensed as 100 mg tablets has increased from 19% to 90%. The percent of patients receiving sertraline 100 mg tablets increased from 26% to 88%.
2. The realized savings for sertraline based on the data from April 1998 and January 1999 is $22,404 per month. The projected annual savings is $268,848, which is more than twice our anticipated savings of $100,000 to $120,000.

Author's Update: Cook County Hospital has been able to maintain its goal of using 100 mg sertraline tablets. In June 1999, 8% of prescriptions for sertraline were dispensed as 50 mg tablets and 92% were dispensed as 100 mg tablets.

MANAGED CARE FORUM

Determining the most economical SSRI for a Medicare risk contract

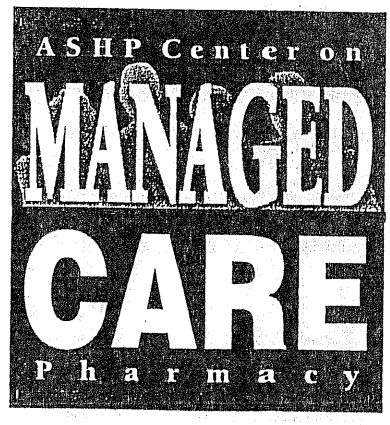
Q: Physicians in our independent practice association have entered into risk-sharing contracts with Medicare for the cost of pharmaceutical therapies. To help manage that risk, I track and report the impact of various drug classes on funds in the pharmacy risk pool. For several years now, I have noted a trend toward increased utilization and costs for antidepressants, largely due to increasing use of selective serotonin-reuptake inhibitors (SSRIs). How should I evaluate SSRIs—mainly fluoxetine, paroxetine, and sertraline—to determine which one has the most favorable pharmacoeconomic profile for a Medicare risk contract?

A: One approach would be to rely on the database-derived evaluations that appear in the literature.[1-8] In looking at that information, however, we realized that our Medicare patients, with an average age of 74 years, differed from the patients described in those studies. Moreover, the total drug costs reported in those evaluations did not match our perception of the cost of treating our Medicare patients.

To get a more accurate view of the total drug cost for treating our Medicare-risk plan members with SSRIs, we selected a sample of members and reviewed their medical charts. Pharmacy claims for members are stored in a computerized database maintained by the HMO with which our physician group contracts. We asked the company to provide a list of the patients enrolled in the Medicare risk plan who had had an SSRI prescription filled during a one-month period. We then completed a chart review to analyze the course of SSRI therapy for each patient selected.

Three hundred forty-two patients were identified, of whom 90 were randomly chosen for chart review: 30 patients receiving fluoxetine, 30 receiving paroxetine, and 30 receiving sertraline. During the chart review, we collected information on patient age and sex; average initial dosage; dosage adjustments required; average maintenance dosage; rate of switching from fluoxetine, paroxetine, or sertraline to an alternative agent; and add-on therapy (anxiolytics or hypnotics). For a majority of the patients, the indication for use of the SSRI was not documented in the chart.

Basis of cost calculations. The software program Therapy Costs (Pfizer Inc., New York, NY) was used to compare and analyze cost data. This pharmacoeconomic program models the cost of therapy on the basis of the acquisition cost of the drug, costs associated with adjusting the dosage of an SSRI (including a $40 physician office visit fee for each adjustment and the cost difference associated with the increased or decreased dosage), costs associated with switching antidepressants (including a physician office visit fee and the acquisition cost of the alternative antidepressant), and costs associated with treating an adverse effect with an add-on medication (including a physician office visit fee and the acquisition cost of the add-on anxiolytic or hypnotic). The flexibility of this program allows cost-input values to be customized.



This column focuses on issues of particular interest to pharmacists who practice in health maintenance organizations and other managed care settings. Other readers should also find the material of interest. Included are information and advice related to managed care pharmacy practice and the use of pharmaceuticals in enrolled patient populations. Topics addressed include disease management, unique pharmacist roles in managed care, capitation, and the ambulatory care component of integrated health systems.

Readers currently practicing in managed care settings are invited to submit questions for the column. Questions should be narrow in scope. Selected questions will be forwarded to one or two practitioners who will prepare brief responses for publication. The inquirers will receive copies of the responses before publication. Readers are encouraged to comment on the answers; such comments will be considered for the Letters column.

Suggestions for topics should be submitted to AJHP, 7272 Wisconsin Avenue, bethesda, MD 20814 (301-657-3000, ext. 1318, or ajhp@ashp.org)

SSRI use. Overall, maintenance dosages increased by 20–30% from the initial dosage in all the SSRI groups. The average initial daily doses for fluoxetine, paroxetine, and sertraline were 16.5, 15.6, and 45 mg, respectively, and the average daily maintenance doses were 23.5, 19.5, and 61.7 mg.

About one third (31%) of the patients required one dosage adjustment; this was most common for patients in the fluoxetine group (40%) and least common in the sertraline group (20%). Seven percent of the patients required a second dosage adjustment; second adjustments were most frequent in the fluoxetine group (13%) and least frequent in the paroxetine group (3%). A majority of the dosage adjustments were upward. Some adjustments were made before the antidepressant effect could be fully noticed (e.g., fluoxetine was adjusted in one patient within one week of the start of therapy). The rate of switching to an alternative antidepressant (74% of the time, to another SSRI) was 33% in the fluoxetine group, 13% in the paroxetine group, and 13% in the sertraline group.

Concomitant anxiolytic use occurred in 14% of the patients (17% of the fluoxetine group, 17% of the paroxetine group, and 10% of the sertraline group). The rate of concomitant hypnotic use was 10% (17%, fluoxetine; 3%, paroxetine; and 10%, sertraline).

Costs. Sertraline is available as scored 50- and 100-mg tablets; patients often split the 100-mg tablets to obtain their individual doses at a lower cost. Since 77% of the sertraline recipients were taking a 50-mg daily maintenance dose, we examined the cost savings that might occur if these patients were prescribed the 100-mg tablet and instructed to take half of a tablet daily. Since a majority of the patients receivingparoxetine were taking 20 mg/day, the benefit of dividing the unscored 40-mg tablet with a tablet splitter was examined. (Fluoxetine is not available as a tablet.)

Overall, costs were highest for fluoxetine therapy; costs for paroxetine were similar to those of sertraline. Splitting paroxetine tablets was more cost-advantageous than splitting sertraline tablets. However, some patients may not be able to use a tablet splitter. Thus, we compared full-tablet paroxetine therapy with split-tablet sertraline therapy and found sertraline to be more cost-effective.

Limitations. Our evaluation was limited by incomplete chart documentation, which required us to make certain assumptions about the patients' therapy. We do not know if the patients were treated with the appropriate dosage for their condition or what percentage of patients were noncompliant. Additional limitations include the relatively small sample size (n = 90), the unknown indirect costs (e.g., costs associated with lost patient or caregiver productivity), the true costs associated with managing adverse drug effects (unknown utilization of nonprescription medications), and the fact that 12 patients were started on an SSRI before entering our health system.

Physician and patient reactions. Physicians were notified of the results of the study through both written communication and one-on-one discussion. Although it is too early to gauge the full impact of our recommendations for SSRI selection and tablet splitting, the physicians and patients appear to have responded positively. One reason our physicians are responsive to pharmacy-related cost and quality issues is that they share part of the financial risk (profit or loss) for the funds set aside in the pharmacy pool. One reason our patients are responsive is that they have a yearly benefit limit (cap). After their benefit limit is exhausted, patients are responsible for the entire cost of their medications.

The organization was able to purchase tablet splitters and provide them to patients at no cost.

Still a place for each SSRI. From our data, it appears that each of the SSRIs evaluated has a role in treating depression in Medicare-eligible patients. Although paroxetine and sertraline have more favorable economics than fluoxetine in our setting, patients complaining of fatigue may benefit from fluoxetine's "stimulating" effect. In patients whose depression has an anxiety component, sertraline may be the desired therapy. In patients who complain of insomnia, paroxetine may be the drug of choice. From a pharmacoeconomic standpoint, if tablets for maintenance doses can be split, considerable savings are possible.

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Dr. Valdez presented this information at the ASHP Annual Meeting, Baltimore, MD, June 3, 1998.

Comparison of Dissolution Between Regular-Release and Halves of Extended-Release Methylphenidate Tablets

JOHN ERRAMOUSPE AND ERIC J JARVI

Objective: To compare the in vitro dissolution of methylphenidate hydrochloride from regular-release tablets to halves of extended-release tablets.

Design: Regular-release 10-mg methylphenidate tablets and halves of 20-mg extended-release tablets from two manufacturers (MD Pharmaceuticals, Inc., and Ciba Pharmaceutical Company) were dissolved according to the USP method specified for regular-release methylphenidate tablets. Samples were collected at 0.25, 0.5, 0.75, 1, 2, 3, 3.5, 4, 5, 6, and 7 hours. Methylphenidate concentration was determined by HPLC.

Results: Regular-release methylphenidate tablets had statistically greater cumulative dissolution at all sample collection times of 2 hours or less compared with halves of extended-release tablets. The most dramatic difference occurred in the first 30 minutes, at which time the difference in cumulative dissolution was 63% (generic) and 55% (Ritalin). At 3 hours and thereafter, there was no significant difference in cumulative dissolution.

Conclusions: Despite being cut in half, extended-release methylphenidate still does not dissolve as fast as regular-release tablets. Halving methylphenidate extended-release tablets may be a clinically acceptable means of achieving a prolonged-acting 10-mg dose.

J Pharm Technol 1998;14:209-11.

In a previous study,[1] the in vitro dissolution of halved extended-release methylphenidate tablets was greater through 6 hours of testing compared with whole extended-release tablets. Although the halved tablets failed the USP test for extended-release tablets,[2] they appeared to retain a slower dissolution, which was expected. In the wax matrix design of the tablet, medication is placed into channels running throughout the tablet and should retain some extended-release characteristics despite being halved. The objective of the present study was to extend the original in vitro dissolution study to include comparison of halves of extended-release methylphenidate tablets to regular-release tablets.

Methods

The USP dissolution method for regular-release methylphenidate tablets was used.[2] The dissolution apparatus consisted of a basket stirring element operated at 100 rpm. A dissolution medium (900 mL of water) was placed in the vessel of the apparatus and equilibrated to 37 °C. One whole 10-mg regular-release generic methylphenidate tablet (MD Pharmaceuticals, Inc., Santa Ana, CA) was placed in the dissolution medium. One-milliliter specimens were removed from the dissolution medium and immediately replaced with 1 mL of water at 0.25, 0.5, 0.75, 1, 2, 3, 3.5, 4, 5, 6, and 7 hours. Before the experiment, a statistician, who had helped analyze the data from the previous study,[1] recommended a sample size of three to five tablets from each manufacturer under each study condition (i.e., halved and whole). A total of six regular-release and three extended-release (i.e., 6 halves from 3 extended-release tablets) tablets were tested. The tablets from each manufacturer were from the same lot number. This procedure was repeated for whole, brand-name, regular-release 10-mg tablets (Ritalin, Ciba Pharmaceutical Co., Summit, NJ) and for halves of 20-mg extended-release tablets for both brand-name (Ritalin-SR) and generic (MD Pharmaceuticals) products. The extended-release tablets were split by using a Pill Splitter EZ Swallow (American Medical Inc., Lake Bluff, IL). Both halves from three split tablets of both the generic and brand-name manufacturers were used. Although previous work had shown no breakdown of methylphenidate stored at room temperature in injection vials over a 24-

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This work was supported by the Faculty Research Committee, Idaho State University, Pocatello, ID (grant 767).

hour period, we elected to be conservative and refrigerate the specimens at 4 °C. Collected specimens were analyzed in batches at the end of every 7-hour collection period. Methylphenidate concentrations were measured by using HPLC as previously described.[1]

The Statistical Analysis System (version 6.1) was used to evaluate the data. A repeated-measures, two-factor ANOVA was used to compare the dissolution percentages for individual specimen collection times. A post hoc Scheffe's test was used to identify where differences occurred between the four study conditions. Statistical significance was determined at the level of p less than 0.05.

Results

Both manufacturers' whole 10-mg regular-release methylphenidate tablets demonstrated statistically greater cumulative dissolution versus halves of extended-release tablets from both manufacturers at sample times of 2 hours or less (Figure 1). The halved extended-release tablets failed the USP test for regular-release tablets.[2] There was no difference between regular-release or halves of extended-release tablets at 3 hours or later.

Discussion

An earlier in vitro dissolution study was performed under specifications for extended-release methylphenidate tablets (i.e., paddle stirring element revolving at 50 rpm in 500 mL of water).[1,2] The present study evaluated in vitro dissolution according to conditions specified for regular-release methylphenidate tablets (i.e., basket stirring element revolving at 100 rpm in 900 mL of water).[2] These latter conditions favored faster dissolution. USP standards require at least 75% in vitro dissolution of regular-release methylphenidate tablets by 45 minutes.[2] Regular-release methylphenidate tablets met this requirement, achieving 91% (Ritalin) and 104% (generic) dissolution at 45 minutes. Halved extended-release methylphenidate tablets dissolved much more slowly, achieving 49% (Ritalin-SR) and 53% (generic) dissolution at 45 minutes. At 3 hours and later, when drug dissolution was greater than approximately 90%, the differences between regular-release and halves of extended-release methylphenidate tablets became insignificant.

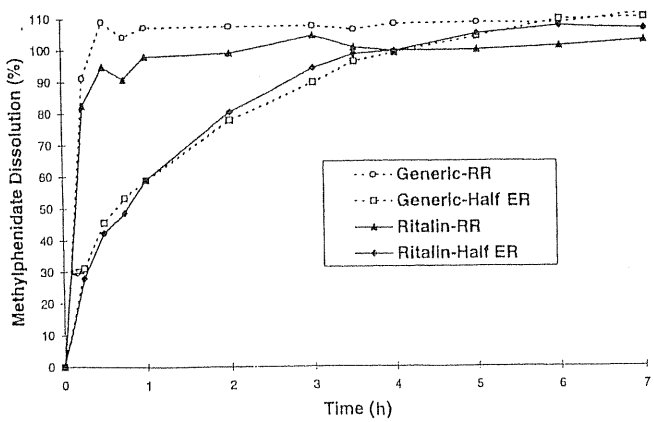

Figure 1. Mean cumulative in vitro dissolution profiles of whole 10-mg regular-release (RR) and halves of extended-release (ER) methylphenidate tablets from two manufacturers. Statistically significant ($p < 0.05$) differences were observed between the profiles of whole RR and halves of ER tablets at all time points of 2 hours or less.

▲

There was no difference between regular-release or halves of extended-release tablets at 3 hours or later.

▼

The slower in vitro dissolution rate of halves of extended-release versus regular-release methylphenidate tablets may correspond to clinical advantages. The incidence of gastrointestinal and appetite suppressant adverse effects may be reduced. Patient compliance could be improved if the duration of control of symptoms of attention-deficit hyperactivity disorder (ADHD) is long enough to permit less frequent dosing (e.g., once daily). Peer ridicule may be lessened or eliminated by avoiding administration of a tablet at school. Also, the hassles of school regulations concerning the administration of medications are avoided.

On the other hand, there are possible clinical disadvantages to using halved extended-release methylphenidate tablets. The minimum dose increment or decrement is 10 mg. Lower dose increments or decrements are possible with regular-release methylphenidate, which is available as a 5-mg tablet. The degree of symptom control for ADHD may be less with extended-release methylphenidate, especially in the first few hours after dose administration. This difference may be due to lower peak concentrations and / or a slower rate of absorption of the extended-release product.[3] In this experiment, regular-release methylphenidate was essentially completely dissolved at 45 minutes, compared with about 50% dissolution for the halved extended-release tablets. The relevance of this loss of peak effect is not known because methylphenidate concentration monitoring has not been shown to be clinically useful.[4] Still, it seems more appropriate to use the regular-release product when rapid control of ADHD symptoms is imperative. However, as discussed previously,[1] comparative trials have not consistently demonstrated the superiority of either dosage form. Practition-

ers are left to determine which dosage form is best for each patient.

▲

...regular-release methylphenidate was essentially completely dissolved at 45 minutes, compared with about 50% dissolution for the halved extended-release tablets.

▼

Finally, clinicians should exercise caution in extrapolating the results of this study to generic versions of methylphenidate not manufactured by MD Pharmaceuticals.

Summary

The cumulative in vitro dissolution of halved extended-release methylphenidate tablets is lower than that of regular-release tablets in the first 2 hours of testing. However, beginning at 3 hours, there is no statistical difference between these dosage forms. Although halving extended-release methylphenidate tablets increases their dissolution rate compared with whole tablets,[1] they still do not dissolve as fast as regular-release tablets. Halving extended-release methylphenidate tablets may be an acceptable clinical solution for achieving a prolonged-acting 10-mg dose. For a few patients, it may be advantageous for tolerance and compliance to halve extended-release methylphenidate tablets rather than convert them to a regular-release product. In vivo investigation is warranted. ≏

We thank Sujit Sansqiry PhD, College of Pharmacy, Idaho State University, for help with the statistical analysis.

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PolicyFinder

H-115.973 Medication Scoring

Our AMA: (1) recommends to pharmaceutical manufacturers that, when appropriate, tablets be scored on both sides and so constructed that they will more readily divide in half and not fragment upon attempts at division; and (2) opposes third party policies that mandate the use of pill-splitting or pill-breaking to reduce pharmaceutical or healthcare costs without proper input from the pharmaceutical manufacturers and practicing physicians. (Res. 51 A-95; Appended: Sub. Res. 513, A-00)

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EFFECT ON DISSOLUTION FROM HALVING METHYLPHENIDATE EXTENDED-RELEASE TABLETS

John Erramouspe and Eric J Jarvi

OBJECTIVE: To determine the effect on in vitro dissolution from cutting methylphenidate extended-release tablets in half.

DESIGN: Ritalin-SR (Ciba Pharmaceutical Co.) and generic methylphenidate extended-release (MD Pharmaceutical Inc.) tablets were dissolved in water according to the method prescribed by the *US Pharmacopeia* under two conditions: whole and halved. Samples were collected at 15, 30, and 45 minutes and at 1, 2, 3, 3.5, 4, 5, 6, and 7 hours. Methylphenidate content was determined by HPLC.

RESULTS: Halving the tablets caused a statistically significant increase in cumulative dissolution as early as 15 minutes. The difference in cumulative dissolution reached its maximum for both Ritalin-SR and generic methylphenidate extended-release tablets at 2 hours. At this time point, the percent dissolution of the whole versus halved tablets was 57% versus 74% (Ritalin-SR), respectively, and 49% versus 67% (generic), respectively. The dissolution profiles of halved and whole extended-release methylphenidate tablets were parallel from this point through the 7-hour collection period. At 7 hours, however, there was no difference in the cumulative dissolution of halved versus whole tablets.

CONCLUSIONS: While statistical differences during in vitro dissolution do exist and pharmacokinetic ramifications have not yet been determined, the absolute differences in dissolution between halved and whole tablets are not great. Halving methylphenidate extended-release tablets may be a clinically acceptable means of achieving a small increment/decrement in dose without converting to a regular-release tablet.

KEY WORDS: methylphenidate, dissolution.

Ann Pharmacother 1997;31:1123-6.

METHYLPHENIDATE regular-release tablets are available in 5-, 10-, and 20-mg strengths, allowing small changes in dose but usually requiring periodic administration two to three times daily.[1,2] Methylphenidate extended-release tablets are available solely in a 20-mg strength and are frequently administered just once daily. Manufacturers[1,2] of methylphenidate extended-release tablets recommend swallowing their products whole to maintain their extended-release dissolution properties. Despite this recommendation, some physicians instruct patients to cut the 20-mg extended-release tablet in half to achieve a 10-mg dose increment/decrement.

Halving the extended-release tablet may alter its dissolution. The tablet, however, is formulated with medication placed into channels running throughout the tablet and may retain some extended-release characteristics despite being halved.[3] If the intended dissolution characteristics of extended-release methylphenidate tablets are not altered significantly, several clinical advantages exist. The need to alternate between regular- and extended-release methylphenidate dosage forms when making changes in dose would be lessened. Noncompliance caused by the more frequent administration requirement and possibly greater gastrointestinal upset of regular-release tablets would be decreased. Peer ridicule secondary to the need to administer doses at school might be avoided. However, if halving these tablets causes too rapid a dissolution of methylphenidate, toxicity could result.

To date, no study has investigated the in vitro dissolution characteristics of extended-release methylphenidate tablets that have been cut in half.[3] Our study compares the dissolution profiles of halved versus whole methylphenidate extended-release tablets.

Methods

The dissolution method described for extended-release methylphenidate tablets in the *US Pharmacopeia* (*USP*) was used in this study.[4] A dissolution apparatus with a paddle stirring element (for extended-release tablets) was used. Five hundred milliliters of water (dissolution medium) was placed in the vessel of the apparatus. The rest of the apparatus was then assembled and the water temperature equilibrated to 37 ± 0.5 °C. One whole 20-mg extended-release generic methylphenidate

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tablet (MD Pharmaceutical Inc.) was placed in the dissolution medium of the apparatus, and the stirrer apparatus started at a rate of 50 revolutions per minute (rpm). Two-milliliter samples were removed from the dissolution medium and replaced with 2 mL of water at 15, 30, and 45 minutes and at 1, 2, 3, 3.5, 4, 5, 6, and 7 hours. Collected samples were placed in sealed injection vials, labeled, stored at room temperature, and analyzed in batches by HPLC at the end of every 7-hour sample collection period. Previous work had shown no breakdown of methylphenidate stored at room temperature in injection vials over a 24-hour period. Prior to the experiment, it had been determined that a minimum sample size of 10 tablets from each manufacturer under each study condition (i.e., halved and whole) would be necessary to detect a difference of 15% or more, assuming a standard deviation of 9% and a power level of 0.992.[5] Twelve tablets were tested of Ritalin-SR (Ciba Pharmaceutical Company) and of methylphenidate extended-release tablets (MD Pharmaceutical Inc.) under each of the study conditions. The tested tablets of each manufacturer were from the same lot number. Two halves from the same split tablet were used for the study condition using halved tablets. The extended-release tablets were split in half by using a Pill Splitter EZ Swallow (American Medical Ind., Lake Bluff, IL). The average percent dissolution of the 12 tablets (percent of the 20-mg labeled dose) for each sample collection time was determined.

Methylphenidate concentrations were measured by using the assay specified by the *USP*.[4] An acetate buffer consisting of anhydrous sodium acetate 0.164% (w/v) was prepared and adjusted to a pH of 4.0 using acetic acid. The mobile phase was then mixed as methanol:acetonitrile: acetate buffer (4:3:3), filtered using a 0.45-µm filter, and degassed. The internal standard, phenylephrine hydrochloride, was dissolved in the mobile phase to a final concentration of 0.4 mg/mL. The methylphenidate standard was prepared by dissolving sufficient USP methylphenidate hydrochloride in mobile phase to make a final concentration of 0.2 mg/mL. The working standard was prepared by transferring 2.0 mL of 0.2-mg/mL methylphenidate standard and 1.0 mL of 0.4-mg/mL phenylephrine internal standard to an HPLC injection vial, capping the vial, and then mixing thoroughly.

Samples were prepared by adding 1.0-mL aliquots to an HPLC injection vial along with 0.5 mL of stock internal standard solution, capping, and mixing thoroughly. Samples and standards were assayed at a flow rate of 1.5 mL/min by using a 25 cm × 4.6 mm (10 µm) nitrile column. The column effluent was monitored by using an ultraviolet detector at 210 nm. Equal volumes (0.50 mL) of samples and standards were injected by using an autosampler. Data were collected and stored by using XCHROM data acquisition software on an RS6000 computer.

The resolution (R_s) between standard and internal standard peaks was maintained at 2.0 or more. The response for each sample and standard was recorded as a peak height ratio (methylphenidate/internal standard). Standards were assayed in triplicate for each batch of samples and a coefficient of variation of 2.0% or less was required. A single analysis of each sample was performed. The quantity of methylphenidate in each sample was calculated from the following formula: $C_u = C_s(R_u/R_s)$, where C_u is the concentration of methylphenidate in the samples, C_s is concentration of the methylphenidate standard, R_u is the peak height ratio response of the sample, and R_s is the mean peak height ratio response obtained from triplicate injections of the working standard solution. The total quantity dissolved was expressed as a percentage of the labeled amount of the original methylphenidate tablets analyzed.

The Statistical Analysis System (SAS, version 6.1) was used to evaluate the data. A repeated-measure two-factor ANOVA was used to compare the dissolution profiles as well as the dissolution percentages for individual specimen collection times. A post hoc Tukey's Studentized range test was used to identify where differences occurred between the four study conditions. Statistical significance was determined at a p value of less than 0.05.

Results

The dissolution profiles of both manufacturers' halved tablets demonstrated statistically greater cumulative dissolution versus whole tablets at all specimen collection times except 7 hours (Figure 1). There was no difference between the mean cumulative dissolution of any of the four study conditions at this last collection time. In addition, halved Ritalin-SR tablets demonstrated significantly greater cumulative dissolution than whole generic tablets at all specimen collection periods except the last. There was no significant difference between the dissolution profiles of the halved generic tablets and the whole Ritalin-SR tablets.

Discussion

Manufacturers of solid dosage forms use a variety of techniques to make extended-release products, including multiple layering, mixed-release pellets, and special matrices.[6] All these techniques attempt to slow the rate of dissolution to achieve an extended duration of effect. Some matrix-based extended-release tablets are scored, and some manufacturers of these tablets (e.g., Theo-Dur, Key Pharmaceuticals, Kenilworth, NJ) have data to support their splitting in half under certain conditions. Manufacturers of methylphenidate extended-release tablets do not score their tablets and have no data to support halving them.

Drug released from matrix tablets involves dissolution of the drug within the matrix and then diffusion out of the matrix.[7] Halving increases the surface area of the tablet where dissolution and subsequent diffusion of the active drug occurs. Intuitively, it seems that halving methylphenidate extended-release tablets should increase their in vitro dissolution. The maximum difference between halved and whole tablets in cumulative percent dissolution occurred at 2 hours for both manufacturers and was around 18% (Figure 1). It is obvious from Figure 1, however, that once this maximum difference in percent dissolution had developed over the first 2 hours, halved extended-release methylphenidate tablets dissolved at a rate similar to that of the whole tablets for the remainder of the study, with one exception. There were no differences noted among any of the four study conditions at the 7-hour measurement.

Early increased in vitro dissolution rate of halved extended-release methylphenidate tablets may correspond

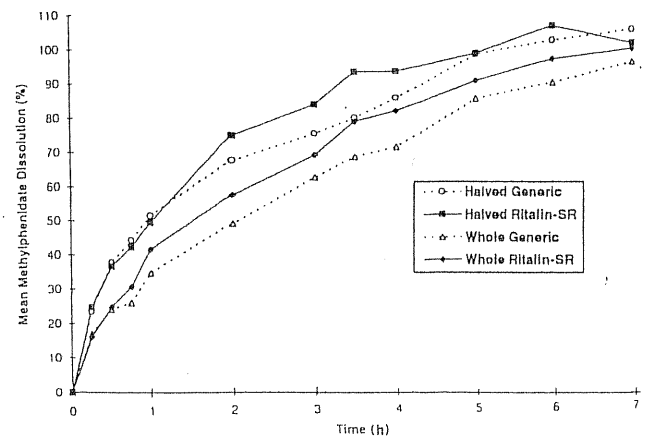

Figure 1. Mean cumulative in vitro dissolution profiles (n = 12 for each profile) of halved and whole methylphenidate extended-release tablets from two manufacturers; statistically significant differences between the profiles of halved and whole tablets from the same manufacturer and between halved Ritalin-SR and whole generic tablets ($p < 0.05$); no significant differences among any of the four study conditions at the final or 7-hour collection period.

with an enhanced in vivo absorption rate. Thus, high methylphenidate plasma concentrations earlier in the dosing interval are possible. Whether this increase is clinically significant for methylphenidate's main indication, attention-deficit hyperactivity disorder (ADHD), is debatable. Monitoring of methylphenidate plasma concentrations has not proven to be clinically useful and there is no established therapeutic range, although a plasma concentration–response relationship has been suggested.[8,9] Clinically, the goals are to maintain adequate attention conducive to learning, especially while the patient is at school, and to minimize possible adverse effects.

An increased in vivo dissolution rate early in the dosing interval may cause more gastrointestinal adverse effects. Taking methylphenidate after meals may lessen gastrointestinal and appetite suppressant adverse effects. One could argue that the potential for gastrointestinal adverse effects from halved extended-release tablets may be less than that experienced secondary to regular-release methylphenidate tablets. At least 75% of a regular-release methylphenidate tablet must dissolve in vitro by 45 minutes to be considered acceptable by the *USP*.[4] In this study, the percentage of methylphenidate dissolved from the halved extended-release tablets averaged only slightly more than 40% at 45 minutes. However, the dissolution methods described for regular- and extended-release methylphenidate tablets in the *USP* differ.[4] This difference favors a faster dissolution for the regular-release tablets because 900 mL of water (vs. 500 mL) is specified as the dissolution medium and the stirring element is specified to rotate at 100 rpm (vs. 50 rpm). Further experiments are planned to compare the in vitro dissolution of regular- versus extended-release tablets.

Using halved extended-release rather than regular-release methylphenidate tablets incurs about the same cost to the patient ($0.51/Ritalin 10-mg tablet vs. $0.56/one-half Ritalin-SR tablet; $0.44/methylphenidate regular-release 10-mg tablet [MD Pharm] vs. $0.49/one-half methylphenidate extended-release tablet [MD Pharm]).[10] The additional dispensing fee for a second prescription of regular-release methylphenidate tablets would probably narrow this slight difference even more.

Companies other than MD Pharmaceutical (i.e., Aligen, Goldline, Major, Novopharm, Parmed, Purepac, Qualitest, Rugby, Schein, Superior) have marketed generic versions of methylphenidate extended-release tablets in the US.[10] To our knowledge, all these generic versions have been made by MD Pharmaceutical. Obviously, clinicians should exercise caution in extrapolating the results of this study to generic versions not manufactured by MD Pharmaceutical that could enter the market in the future.

The perceived compliance or pharmacokinetic advantage of extended-release methylphenidate tablets is important to some physicians. Some physicians may prefer to prescribe the extended-release tablet to maximize patient compliance through less frequent administration (typically once daily). This strategy avoids having to administer a tablet at school and the risk of peer ridicule. Also, some school officials refuse to allow school personnel involvement in administering medication.[8]

Five double-blind studies[11-15] have investigated the claim of equivalence between extended- and regular-release methylphenidate in the treatment of ADHD. Two studies reported a lack of significant difference in efficacy between these two dosage forms.[11,12] Whitehouse et al.[13] found the control of conduct problems to be better with regular-release methylphenidate, based on results of a teacher questionnaire, but a questionnaire completed by parents statistically favored extended-release methylphenidate. Although not clearly reported, the presumed proximity of medication administration to the time of observation may explain these disparate results. Typically, teachers observe children in the morning and early afternoon shortly after medication administration, when regular-release methylphenidate might have an advantage because of a quicker onset. Parents usually view children in the late afternoon and evening, long after medication administration, when extended-release methylphenidate might still be acting. Pelham et al.[14] reported that regular-release methylphenidate has a shorter onset for benefiting continuous performance tasks (1 h vs. 3 h onset) and is statistically superior in decreasing noncompliance and negative verbalizations compared with extended-release methylphenidate. Surprisingly, Pelham et al.[15] found regular-release methylphenidate to manifest a longer onset of effect for continuous performance tasks than did extended-release methylphenidate (2 h vs. 1 h onset). Since some studies[13-15] performed to date suggest crucial differences between these two dosage forms, practitioners should determine on an individual basis which dosage form is best.

Summary

The in vitro dissolution profile of extended-release methylphenidate tablets is altered by cutting them in half, as is apparent from an increase in cumulative dissolution as early as 15 minutes. The difference in cumulative dissolution for whole versus halved tablets reached its maximum at 2 hours (Ritalin-SR 57% vs. 74%, respectively, generic tablets 49% vs. 67%, respectively). Thereafter, the dissolution profiles of halved and whole extended-release methylphenidate tablets were parallel, reaching essentially 100% dissolution by the end of the 7-hour collection period. At 7 hours there was no difference in the cumulative dissolution of halved versus whole tablets.

Despite differences in the halved versus whole tablets in vitro dissolution profiles, halved extended-release methylphenidate tablets may be a clinically viable method of achieving smaller changes in dose without converting a patient's therapy to a regular-release tablet. Further investigation is warranted. ≃

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EXTRACTO

OBJETIVO: Determinar el efecto en la disolución in vitro al cortar por la mitad tabletas de liberación extendida de metilfenidato.

DISEÑO: Ritalin-SR y tabletas de liberación extendida de metilfenidato genérico (MD Pharmaceutical Inc.) fueron disueltas en agua de acuerdo al método prescrito por la Farmacopea de los Estados Unidos bajo dos condiciones, completas y cortadas por la mitad. Muestras fueron coleccionadas a los 15, 30, y 45 minutos y a 1, 2, 3, 3.5, 4, 5, 6, y 7 horas. El contenido de metilfenidato fue determinado a través de HPLC.

RESULTADOS: El cortar las tabletas por la mitad ocasionó un aumento en la disolución cumulativa estadísticamente significativo tan pronto como 15 minutos. La diferencia en disolución cumulativa alcanzó su máximo a las 2 horas para ambos, Ritalin-SR y tabletas de liberación extendida de metilfe nidato genérico. A este punto en tiempo, el por ciento de disolución de las tabletas completas contra las tabletas cortadas por la mitad fue de 57% contra 74% (Ritalin-SR) y 49% contra 67% (genérico). Los perfiles de disolución de las tabletas de liberación extendida de metilfenidato cortadas por la mitad y enteras se igualaron desde este punto a través del período de colección de 7 horas. A las 7 horas sin embargo, no hubo diferencia en la disolución cumulativa de las tabletas cortadas por la mitad contra las tabletas enteras.

CONCLUSIONES: Mientras que existen diferencias estadísticas durante la disolución in vitro y aún no se han determinado las ramificaciones farmacocinéticas, las diferencias absolutas en disolución entre las tabletas cortadas por la mitad y las tabletas enteras no son grandes. El cortar las tabletas de liberación extendida de metilfenidato podría ser una manera clínicamente aceptable de alcanzar un pequeño incremento/decremento en dosis sin cambiar a una tableta de liberación corriente.

BRENDA R MORAND

RÉSUMÉ

OBJECTIF: Déterminer les effets sur la dissolution in vitro d'une brisure en deux moitiés de comprimés de méthylphénidate à action prolongée.

DEVIS EXPÉRIMENTAL: Des comprimés à libération prolongée de Ritalin-SR et d'un produit générique (MD Pharmaceutical Inc.) ont été dissous dans de l'eau selon le procédé décrit dans la pharmacopée américaine sous deux conditions, entiers et coupés en deux. Des échantillons ont été prélevés à 15, 30, et 45 minutes, ainsi qu'à 1, 2, 3, 3.5, 4, 5, 6, et 7 heures. La teneur en méthylphénidate a été mesurée par chromatographie liquide à haute pression.

RÉSULTATS: Scinder les comprimés en deux a causé une augmentation statistiquement significative de la dissolution cumulative et ce, aussi tôt que dans les premières 15 minutes. La différence maximale dans la dissolution cumulative a été obtenue pour le Ritalin-SR et le produit générique à 2 heures. À ce moment, le taux de dissolution du comprimé entier contre la demie était 57% contre 74% (Ritalin-SR) et 49% contre 67% (générique). Les profils de dissolution des comprimés entiers et des moitiés de comprimés sont parallèles des échantillons pris à 2 heures jusqu'à ceux pris à 7 heures. À 7 heures, cependant, il n'y avait pas de différence dans la dissolution cumulative entre les comprimés entiers et ceux scindés.

CONCLUSIONS: Alors que des différences statistiques existent lors de la dissolution in vitro et que les implications pharmacocinétiques n'ont pas encore été déterminées, les différences absolues dans la dissolution entre les comprimés entiers ou scindés en deux sont faibles. Couper en deux les comprimés à libération prolongée de méthylphénidate peut être acceptable cliniquement afin d'effectuer de petites augmentations ou diminutions de posologie sans revenir à la formulation régulière.

DENYSE DEMERS

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Effect of tablet integrity on the dissolution rate of sustained-release preparations

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SUMMARY

The objective of this study was to evaluate the effect of tablet integrity on the dissolution rate. The model drug used for this study was aspirin. A dissolution study was performed with three commercially-available aspirin tablets (ZORprin®, Bayer® 8-h aspirin and Bayer® aspirin), two of which were sustained-release tablets. For ZORprin®, the average dissolution data indicated that the *in vitro* release rate of aspirin was consistent with the intended design of the sustained-release wax matrix tablets only when the tablets were intact. The split tablets showed a consistently higher release profile over time, with a 50% higher release at 6 h. However, the Bayer® 8-h aspirin and plain aspirin tablet data showed that tablet integrity had no significant impact on the dissolution rate, because the intact and split tablets showed similar drug release profiles over time. In conclusion, care should be taken to administer sustained-release tablets, avoiding any breaking or crushing of the tablets unless this is directed by the manufacturer.

INTRODUCTION

A sustained-release preparation is designed to deliver an amount of drug sufficient to cause the desired therapeutic response immediately following the administration, and then to slowly release the rest of the dose over the next few hours. Use of sustained-release preparations provides an excellent tool to achieve precise control of the drug release mechanism (1–5). The drug release mechanism can be controlled by carefully fabricating the system (6). The fabrication procedure involves the use of a suitable water soluble or water insoluble polymer along with the drug. Depending on the fabrication procedures the final sustained-release preparation can be a mixture of coated pellets, a mixture of polymer/drug granules, non-disintegrating tablets, matrix tablets, tableted microcapsules, or microcapsules (4). The drug release characteristic is dependent on the specific prolonged action mechanism utilized in manufacturing the sustained-release preparation (7–10). Many drugs have been formulated into controlled-release preparations. These preparations require less frequent administration and improve patient compliance. When administered to patients who have difficulties swallowing whole tablets or capsules, however, controlled-release formulations may pose a serious risk. Crushing these products may cause an immediate release of large quantities of the drug (dose dumping).

The objective of this study was to evaluate the effect of tablet integrity on the dissolution rate. The model drug used for this study was aspirin. Aspirin is available commercially as plain tablets as well as sustained-release tablets. The different sustained-release aspirin tablets also differ in their drug release mechanism. Some of the aspirin preparations are matrix tablets and some are microencapsulated aspirin compressed into tablets.

MATERIALS AND METHODS

Materials

The following dosage forms of aspirin were purchased from retail outlets:

1. Sustained-release tablets each containing 800 mg aspirin as a matrix tablet (ZORprin®, Boots Pharmaceuticals, IL, U.S.A.).
2. Sustained-release tablets each containing 650 mg extended release aspirin as microencapsulated

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particles (Bayer® 8-h aspirin, The Bayer Co., NY, U.S.A.).

3. Plain aspirin tablets each containing 325 mg aspirin (Genuine Bayer® aspirin, The Bayer Co., NY, U.S.A.).

Aspirin standard and hydrochloric acid was purchased from Sigma Chemical Co., MO, U.S.A.

Methods

Aspirin standard curve. A calibration curve was prepared by measuring the absorbance of nine standard solutions containing 1, 5, 10, 20, 30, 50, 70, 90 and 100 μg of aspirin per 1 ml of the solution (in 0·1 N HCl). The absorbency was measured at 278 nm in a spectrophotometer (DU 640, Beckman, CA, U.S.A.). Each point on the calibration curve was based on three determinations. The concentration–absorbency relationship was linear (r=0·9998) over the studied range.

Dissolution. Six individual tablets from the same lot of each formulation were used for the dissolution study. Three tablets from each formulation were cut in half using an EZ tablet cutter, while the other three were left intact. The dissolution studies of the split and intact tablets were performed at 37 ± 1°C using the rotating paddle dissolution apparatus (Vanderkamp 600, Vankel Industries, NJ, U.S.A.) at 50 rpm stirring speed. The dissolution experiments were performed in triplicate. The dissolution medium consisted of 1000 ml of 0·1 N HCl, which was de-aerated before use. After the introduction of the tablets, 1 ml samples were collected at various times by means of a filter pipette. For ZORprin® tablets, sampling was continued for up to 6 h (sampling at 5, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min). Whereas sampling was terminated at 4 h and 2 h for the Bayer® aspirin tablets (sampling at 5, 15, 30, 45, 60, 90, 120, 180 and 240 min) and the plain aspirin tablets (sampling at 5, 10, 15, 30, 45, 60, 90 and 120 min), respectively.

Analysis. The dissolution samples were diluted ten times with 0·1 N HCl before analysis. The amount of aspirin in solution at any time was determined by measuring the absorbance of the diluted samples at 278 nm in a spectrophotometer (DU 640). The concentration of aspirin in the solution was determined by the calibration curve.

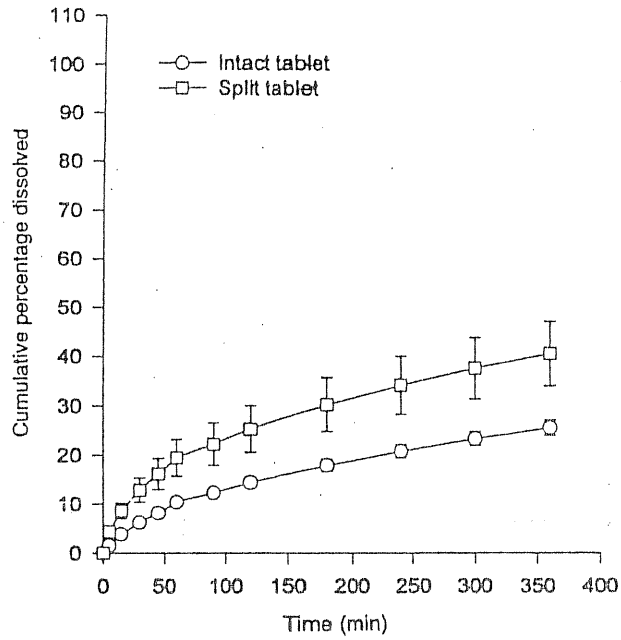

Fig. 1. Dissolution profiles of ZORprin® tablets (n=3).

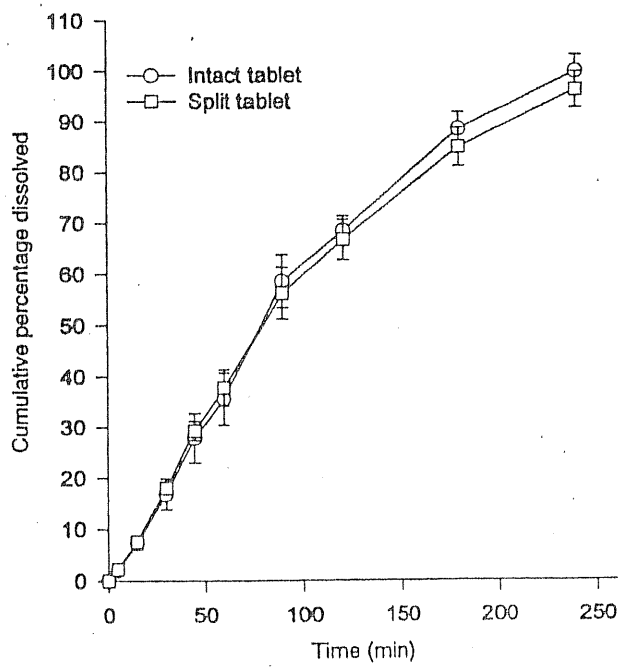

Fig. 2. Dissolution profiles of Bayer® 8-h aspirin tablets (n=3).

RESULTS AND DISCUSSION

The dissolution of aspirin was compared by calculating the cumulative percentage of the drug released at a specific sampling time. Figures 1–3 show the dissolution profiles of the three different aspirin preparations.

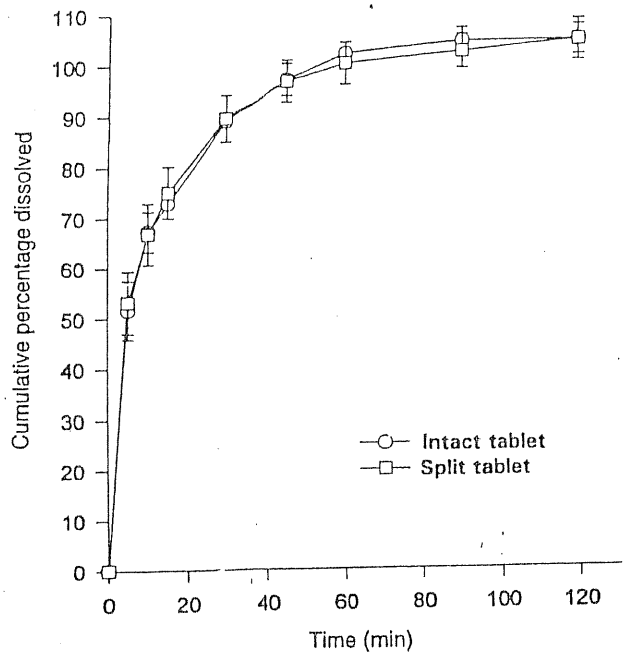

Fig. 3. Dissolution profiles of Bayer® plain aspirin tablets ($n=3$).

For ZORprin®, the average dissolution data indicated that the *in vitro* release rate of aspirin was consistent with the intended design of the sustained-release wax matrix tablets only when the tablets were intact. The split tablets showed a consistently higher release profile over time, with a 50% higher release at 6 h (Fig. 1). However, the Bayer® 8-h aspirin and plain aspirin tablet data showed that tablet integrity had no significant impact on the dissolution rate, because the intact and split tablets showed similar drug release profiles over time (Figs 2–3). A comparison of the dissolution profiles of the intact and split ZORprin® tablets also revealed that the SD associated with the dissolution data of the split tablets was significantly higher than that of the intact tablets. This high SD value for split ZORprin® tablets also proves that the split tablets had less reproducible results compared with the intact tablets.

Both Bayer® 8-h and ZORprin®, as controlled-release formulations, had lower dissolution rates than the regular release Bayer® aspirin. Bayer® 8-h tablets contain microencapsulated aspirin. According to the manufacturer, this tablet may be broken in half for administration. The microencapsulation of aspirin particles slows their release and the release profile is not dependent on tablet integrity. Whereas, ZORprin® tablets contain aspirin within a slowly eroding matrix. Breaking these tablets will disrupt the matrix structure and greatly increase the amount of drug exposed to the dissolution medium. Higher dissolution rates are the expected result of any loss of tablet integrity.

The results of this study underline the importance of proper administration of all medications. Whether self-administered or administered by a caretaker/health professional, medications should only be given as directed. As drug information specialists, pharmacists should know which medications must not be crushed. Care should be taken to administer sustained-release tablets, avoiding any breaking or crushing of the tablets unless this is directed by the manufacturer.

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The tablet splitter: Barrier to compliance or cost-saving instrument?

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Am J Health-Syst Pharm. 1995; 52:2707-8

Traditionally, tablet splitters have been provided to patients when a tablet is too large to swallow easily or when a smaller dose is needed. A third reason for using these devices is to cut costs. At an Air Force medical center in northern California, the procurement cost of lovastatin 40-mg tablets is less than twice that of 20-mg tablets. To decrease drug acquisition costs, the pharmacy supplies patients prescribed lovastatin 20 mg daily with 40-mg tablets and a tablet splitter (Figure 1) and instructs them to take one half tablet every day. (The device is manufactured by LGS Corporation and distributed by Health Care Logistics, Inc., Circleville, OH.)

Our search of the medical and pharmacy literature revealed no information on the effect of tablet splitters on compliance or on patients' acceptance of these devices. We conducted a survey to assess patients' impressions of and experiences with the tablet splitter.

Methods. This project was approved by the institutional review board. To identify patients for the survey, we searched prescription records from April 1993 through October 1994, cross-referencing prescriptions for tablet splitters and lovastatin 40 mg with "one half" or "20 mg" in the prescription instructions; we found 318 eligible patients. We developed a questionnaire, which was reviewed by a biostatistician, tested on several patients, revised, and mailed to all 318 patients.

Patients' responses were entered into a Microsoft Excel Version 4.0 spreadsheet and analyzed with Crunch Version 4.0 Statistical Software. Responses were evaluated to determine whether age, sex, or number of prescribed drugs affected patients' responses.

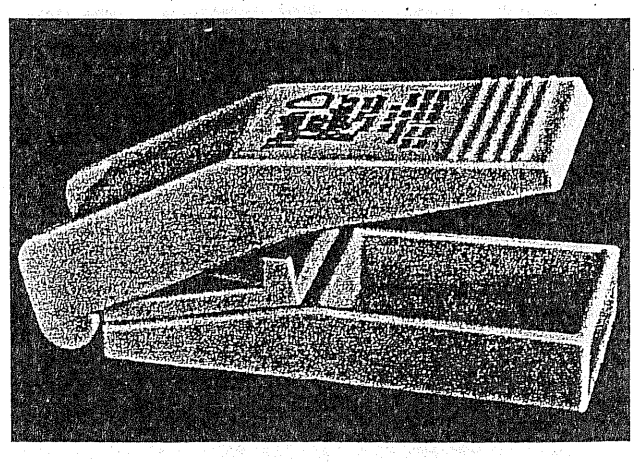
Results and discussion. Two-hundred thirty-three usable surveys (73%) were returned. Eighty-four percent of respondents were 55 years or older, with a mean age of 65 years (standard deviation, 9.9 years; range, 35–87 years). Fifty-two percent were women. Respondents were prescribed an average of 4.4 medications and took an average of six doses per day.

The survey questions and responses are shown in the appendix. Most patients said the tablet splitter was easy to use, did not waste medication, and did not affect their compliance. Interestingly, 6% reported that the tablet splitter was not easy to use, that they would not use one even if it would save them money, and that the tablet splitter discouraged them from complying with their prescribed regimen. A mechanism is needed for prospectively identifying patients unwilling or unable to use the tablet splitter.

The concern most frequently cited was that the tablet splitter did not consistently produce two equal doses. In some clinical situations, dosing must be precise. However, when slight dose variations associated with split tablets are acceptable, patients should be reassured of this.

We identified three limitations of this study. First, because responses were anonymous, we could not check reported compliance against the patients' medication profiles. Furthermore, question 7, concerning missed doses, produced only 150 usable responses. Many patients wrote "zero" in the blank rather than selecting an answer option, which may indicate that they were exaggerating their compliance. Second, we evaluated use of the tablet splitter with only one medication, lovastatin; responses could differ if other medications were evaluated. Third, the patients we surveyed were all active and retired military personnel and spouses. This group receives free prescriptions and may differ from the general population in other ways

Figure 1. Tablet splitter.



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The views expressed here are those of the authors and do not reflect the official policy or position of the U.S. government, the Department of Defense, or the Department of the Air Force.

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that prevent extrapolation of the results.

Conclusion. A majority of respondents found tablet splitters easy to use and said they did not hinder compliance, although it is not known whether tablet splitters saved money or what the actual effects on compliance were. When tablet splitters are used to reduce drug costs, pharmacists should assess patients' abilities and concerns.

Appendix—Questions and percentages of responses in each category

1. The tablet splitter is easy to use. (n = 226)

Strongly agree	Agree	Mildly agree	Mildly disagree	Disagree	Strongly disagree
41.6	45.6	6.6	0.4	4.9	0.9

2. The tablet splitter always cuts the tablet into close-to-equal halves. (n = 229)

Strongly agree	Agree	Mildly agree	Mildly disagree	Disagree	Strongly disagree
21.4	41.5	16.6	6.6	7.4	6.6

3. How many times during the last month did the tablet splitter damage the tablet so that you were not comfortable taking the dose (one or both halves)? (n = 226)

Seldom	1–2 Times	3–4 Times	5–6 Times	>6 Times
56.6	15.0	13.7	5.8	8.9

4. How many times in the last month did you drop a tablet (one or both halves) while trying to cut it or just after cutting it? (n = 227)

Seldom	1–2 Times	3–4 Times	5–6 Times	>6 Times
76.7	11.9	9.3	0.4	1.8

5. How many times in the last month did you throw away a tablet (one or both halves) because you dropped it while trying to cut it or just after cutting it? (n = 225)

Seldom	1–2 Times	3–4 Times	5–6 Times	>6 Times
85.3	10.2	2.7	0.4	1.3

6. How long did it take you to cut your last tablet in half? (n = 228)

<1 Minute	1–2 Minutes	3–4 Minutes	5–6 Minutes	>6 Minutes
93.0	4.8	1.3	0.4	0.4

7. Compared with my other medications that I do not have to cut in half, I miss ___ doses in a month. (n = 150)

Many more	More	Slightly more	About the same	Slightly harder	Many fewer
1.3	4.7	8.0	37.3	1.3	34.7

8. Tablets cut in half are ___ to take than whole tablets. (n = 226)

Much easier	Easier	Slightly easier	About the same	Slightly harder	Harder	Much harder
15.0	18.6	1.8	54.0	4.9	4.0	1.8

9. The tablet splitter has had no effect on my willingness to take lovastatin as prescribed. (n = 225)

Strongly agree	Agree	Mildly agree	Mildly disagree	Disagree	Strongly disagree
47.1	42.2	4.4	1.8	3.6	0.9

10. The use of the tablet splitter was adequately explained to me. (n = 223)

Strongly agree	Agree	Mildly agree	Mildly disagree	Disagree	Strongly disagree
21.0	42.2	5.4	1.4	17.5	12.6

11. The directions for cutting my dose of lovastatin were adequately discussed with me. (n = 224)

Strongly agree	Agree	Mildly agree	Mildly disagree	Disagree	Strongly disagree
21.0	37.1	4.0	2.2	22.8	13.0

12. Imagine that you are in the situation of having to pay for your prescriptions. Please rate the following statement: "If the tablet splitter could save me money, I would use one." (n = 227)

Strongly agree	Agree	Mildly agree	Mildly disagree	Disagree	Strongly disagree
53.7	37.0	3.1	1.3	2.6	2.2

LETTERS

Splitting tablets in half

Some tablets cannot be easily divided in half because of size, shallow score line, or thickness. Other tablets are not intended by the manufacturer to be broken in half; however, doses of some drugs for pediatric or geriatric patients may necessitate the use of half tablets. To assure ourselves that patients would receive half tablets containing about half of the labeled amount, we evaluated a tablet-splitting device for accuracy.

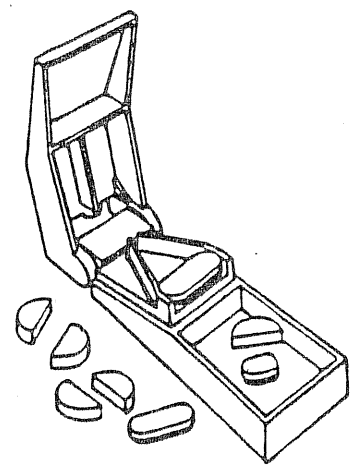
The Pill Splitter (LGS Health Products, Beachwood, OH) is a rigid plastic box with an incline that includes a V-shaped partition on which the tablet sits (figure). The attached lid has a steel blade that cuts the tablet when the box is closed. We used tablets of various shapes and sizes (round or oblong, flat or oval, plain or coated, scored or not scored) for the evaluation. We weighed 20 tablets of each type, cut them in two with the device, and then weighed the two parts.

Pefloxacin (Roger Bellon), sulfasalazine (Pharmacia), and aluminum hydroxide (Rorer) half tablets were all within 15% of their respective mean weights; however the aluminum hydroxide tablets were friable and broke into more than two parts on several occasions. The pefloxacin and sulfasalazine tablets were large (18.3 × 9.3 × 4.7 mm, 780 mg, and 18.2 × 9.2 × 5.7 mm, 670 mg, respectively), with oblong shapes and flat sides. These characteristics made the tablets easy to insert in the device.

One each of the nifedipine 20 mg (Bayer Pharma), nitroxoline (Debat), phloroglucinol (Lafon), and dexamethasone (Roussel) half tablets was >15% of its respective mean half-tablet weight. All these tablets were coated except dexamethasone. The dexamethasone tablets had a deep score line, but it was

Continued on page 550

Tablet-splitting device.



The Letters *column is a forum for rapid exchange of ideas among readers of* AJHP. *Liberal criteria are applied in the review of submissions to encourage contributions to this column.*

The Letters *column includes the following types of contributions: (1) comments, addenda, and minor updates on previously published work, (2) alerts on potential problems in practice, (3) observations or comments on trends in drug use, (4) opinions on apparent trends or controversies in drug therapy or clinical research, (5) opinions on public health issues of interest to pharmacists in health systems, (6) comments on ASHP activities, and (7) human interest items about life as a pharmacist.*

Short papers on practice innovations and other original work are included in the Notes *section rather than in* Letters.

Letters need not be submitted with AJHP*'s manuscript checklist. The following conditions, however, must be adhered to: (1) the body of the letter must be no longer than two typewritten pages, (2) the use of references and tables should be minimized, (3) the number of authors should be no more than three, (4) the authors' names, affiliations, and mailing addresses must be typed at the end of the letter in the format used by* AJHP, *and (5) the entire letter (including references, tables, and authors' names) must be typed double-spaced on plain white paper (not letterhead). Following acceptance of a letter, the authors are required to sign an exclusive publication statement and a copyright transferal form. All letters are subject to revision by the editors. Authors do not receive proofs of edited letters.*

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Colony-stimulating factors cannot be directly compared

In the supplement to the July 1993 issue of *AJHP*, Louie and Jung[1] reviewed the clinical effects of biologic response modifiers. However, practitioners reading this review may be misled as to the comparative safety and efficacy of filgrastim, sargramostim, and regramostim.

Filgrastim (Neupogen, Amgen Inc., Thousand Oaks, CA) is granulocyte colony-stimulating factor (G-CSF) expressed in *Escherichia coli*; sargramostim (Leukine, Immunex Corporation, Seattle, WA) is granulocyte–macrophage colony-stimulating factor (GM-CSF) expressed in yeast; and regramostim is GM-CSF expressed in Chinese hamster ovary cells. No trials comparing the safety and efficacy of these agents have been published. Louie and Jung's comparisons of the colony-stimulating factors (CSFs) were based on the results of studies with various designs and doses, conducted in patients with a wide variety of diagnoses and severity of illnesses.

In Table 1, Louie and Jung compared the adverse-effect profiles of sargramostim and filgrastim. However, the authors did not clearly indicate that the data were obtained from markedly different patient groups. Sargramostim patients had undergone bone marrow transplantation and received the drug to enhance neutrophil recovery after transplantation.[2] Filgrastim patients had been treated with antineoplastic agents and had received filgrastim because they were at risk of developing chemotherapy-induced neutropenia.[3] Furthermore, the data reported for sargramostim were expressed as the percentage of patients receiving the indicated therapy who experienced adverse effects, whereas the data for filgrastim were expressed as the percentage of treatment-blinded cycles in which adverse events occurred. Because the frequencies of adverse events were measured differently, the percentages listed in Table 1 should not be compared, despite their side-by-side placement. Rather, readers should compare the frequencies of adverse events reported for each CSF versus placebo to determine if the administration of the CSF is likely to increase the risk of an individual adverse event in the patient population under study. Viewing the data in this way, the clinician can see that neither CSF resulted in a notably higher frequency of adverse effects than placebo.

Table 1 also contained a misprint for the occurrence of fever in patients receiving sargramostim (95%) versus placebo (the correct percentage is 96%[4]) and incomplete data for filgrastim. The data shown for fever associated with filgrastim therapy included neutropenic fever only; however, the filgrastim package insert reports the data for fever and neutropenic fever separately.[5] The frequencies of both adverse effects should have been reported in the table.

Louis and Jung also stated that there is a high incidence of chills in patients treated with GM-CSF, but chills was not listed in Table 1 or in the package inserts. The authors did not state how they determined which adverse events to list. Their failure to include the frequency of pain associated with sargramostim therapy (0% of patients treated with sargramostim or placebo) or with filgrastim therapy (24% of cycles with filgrastim and 18% of cycles with placebo) is an important oversight.

G-CSF and GM-CSF can be expressed in a variety of biological systems, and the specific system may be an important factor in determining safety and efficacy.[6] Therefore, comparative data on CSFs should be reviewed with caution. Unfortunately, not only are there no comparative clinical trials of the CSFs, there are no large, randomized, double-blind, prospective, placebo-controlled trials conducted in patient groups or for indications that are similar enough to allow clinicians to make a balanced comparison of CSF safety and efficacy.

1. Louie SG, Jung B. Clinical effects of biologic response modifiers. *Am J Hosp Pharm.* 1993; 50(Suppl 3):S10-8.
2. Nemunaitis J, Rabinowe SN, Singer JW et al. Recombinant granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid

Continued on page 552

Splitting tablets

Continued from page 548

difficult to position the blade directly on the score line and get a clean cut.

The ethambutol (Lederle), acyclovir 200 mg (Wellcome), magnesium plus pyridoxine (Millot-Solac), fusidic acid (Leo), nystatin (Bristol Myers Squibb), pyridostigmine (Produits Roche), and phenobarbital 10 mg (Specia) half tablets were sometimes (4–11 of the 40 halves) >15% of their respective mean weights. The phenobarbital tablets were the smallest (diameter, 4.1 mm) and lightest (30 mg) tablets tested. The magnesium plus pyridoxine and fusidic acid tablets were oblong with rounded edges, leading to difficulties in placing the tablets properly in the device; the nystatin tablets were round with rounded edges.

The device easily cut all of the tablets. We had the best results with the larger tablets (>600 mg) and those that were coated, were oblong but not pointed, and had flat edges.

Users of the device must take precautions to avoid exposing persons to drugs they are allergic to (e.g., penicillin powder should be wiped off the device) and to avoid cutting themselves when placing tablets in the device or removing tablet pieces.

The use of half tablets cannot replace elegantly prepared suspensions and other liquid preparations for pediatric patients, but half tablets might be useful for twice-a-day treatments with drugs having wide therapeutic windows.

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Making It Easier to Swallow

Patients who can't swallow pills or tablets whole need not use razor blades and hammers to cut and crush their medications. Compact pill splitters and crushers can do the job for them.

Eileen M. McCormick

Some people can swallow a handful of pills in one easy gulp, while others cannot consume even one small pill unless it is crushed and mixed with liquid or food. For the latter group, taking prescription or OTC medications can be a frustrating experience which, in a worst case scenario, can lead to serious noncompliance with prescribed therapy.

Help for Select Patients

Elderly or arthritic patients who have tried splitting a slippery pill with a kitchen paring knife—and parents who have struggled to pulverize a child's medication between two pieces of waxed paper with the aid of a rolling pin—will be beneficiaries of three products manufactured by American Medical Industries (AMI): The EZ-Swallow Pill Crusher, the EZ-Swallow Pill Splitter, and the EZ-Swallow Combo Unit which combines the two operations in one small plastic container. Although the pill crusher has been marketed for some time, the pill splitter and combo unit are recent additions to the EZ-Swallow line.

Dan Anderson, Executive Vice President and Director of AMI, believes the pill crusher is especially helpful for children, people with arthritis, invalids, elderly patients, or anyone who finds swallowing pills inconvenient and uncomfortable. He also notes that many animal owners use the pill crusher to help them give medication and vitamin supplements to their pets. All three products are dishwasher-safe.

- The *EZ-Swallow Pill Crusher,* which has a large capacity for oversize pills and tablets, is a specially designed container that does triple duty, i.e., it stores the pills, crushes them, and provides a drinking vessel all in one easy-to-carry unit.
- The *EZ-Swallow Pill Splitter* converts tablet medications or vitamins into smaller dosages quickly and safely. This pocket- or purse-sized splitter features a stainless steel blade housed in a positive locking lid for safety and a built-in storage compartment with a friction fit cap which prevents pills from spilling out.
- The *EZ-Swallow Combination Pill Splitter/Pill Crusher* offers the patient the best of both worlds

in one convenient package. The combo has three sections, i.e., the top unit which houses the stainless steel blade, the center portion which serves as a storage container for tablets and doubles as a mixing/drinking vessel, and the bottom section which is a threaded pill crusher that can be effectively used even by arthritic patients or those with limited hand/wrist strength.

Although the blade in the pill splitter is not replaceable, Anderson says that he repeatedly used the same unit for display purposes at a number of trade shows. Even after splitting thousands of pills, the blade continued to work quickly and efficiently. He attributes this longevity to the fact that the EZ-Swallow Pill Splitter uses a surgical stainless steel rather than a carbon blade and, for this reason, it stays sharper longer and does not rust.

Anderson notes that DRG-conscious hospitals are increasingly concerned that noncompliance with prescribed therapy—for whatever reason—may cause patients who have been discharged to require readmission, a costly procedure for the hospital. Institutions such as Humana Hospitals have expressed interest in using the EZ-Swallow Pill Crusher and EZ-Swallow Pill Splitter for those patients who cannot swallow whole tablets or pills. The device, which would be charged to the patient, would be used during hospitalization and then sent home with the patient after instruction from hospital personnel about its proper use. Hospitals see this as a way of improving therapy compliance in this select group of patients. (PT)

BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 10, 311–319 (1989)

MULTIPLE DOSE COMPARISON OF A WHOLE 240 mg VERAPAMIL SUSTAINED-RELEASE TABLET WITH TWO HALF TABLETS

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ABSTRACT

Twelve healthy male volunteers were studied in a balanced crossover comparison of an intact 240 mg verapamil sustained-release tablet (Securon SR, Isoptin Forte Retard) given once daily for 7 days, and the same dose given as two half tablets. One subject was withdrawn because of asymptomatic second degree heart block on day 3 of verapamil treatment. The mean C_{max} after dosing with whole tablets, 143 (95 per cent confidence limits 91·6–223) ng ml^{-1} was lower than after dosing with half tablets, 160 (107–241) ng ml^{-1}, but this was not significant (p=0·49). The mean steady-state C_{min} values after whole and half tablets were also similar: 22·2 (12·6–39·4) ng ml^{-1} and 22·0 (16·2–29·9) ng ml^{-1}, respectively (p=0·96). The mean (±S.D.) t_{max}, AUC_{0-24} and $t_{½}$ were not significantly different: whole tablet 3·5 ± 1·2 h, 1733 ± 1125 ng.h ml^{-1} and 10·5 ± 3·4 h, respectively, and half tablets 3·6 ± 1·0 h, 1780 ± 1057 ng.h ml^{-1} and 9·6 ± 2·3 h, respectively. The findings for plasma norverapamil were generally similar to those for the parent drug. This investigation indicates that the formulation is sufficiently robust to retain its sustained-release properties when the tablet is halved.

KEY WORDS Sustained-release Pharmacokinetics Steady-state Verapamil Norverapamil

INTRODUCTION

Verapamil is an antihypertensive, antianginal and antiarrhythmic calcium channel blocking agent for which a 240 mg sustained-release scored tablet formulation has recently been developed (Securon SR, Isoptin Forte Retard). This could simplify chronic verapamil medication by allowing once-daily dosage. Previous studies using twice-daily dosing of this sustained-release formulation have shown that peak to trough ratios are considerably less than those found with the conventional release preparation.[1] Greater dosage flexibility (dose units of 120 mg) would be achieved if the tablet could be broken along the score. In order to support the use of half tablets of a sophisticated

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sustained-release formulation it is necessary to determine whether intact and broken tablets give a comparable pharmacokinetic profile.

The present study was carried out to characterize the plasma level profile of the sustained-release preparation under multiple dose conditions and to compare plasma levels after the intact 240 mg tablet with those after the same total dose as two halves of the same formulation.

METHODS

Subjects

Twelve healthy male subjects aged 20–34 years and within 15 per cent of normal weight for height (range 61·3–98·0 kg) entered the study which was approved by the University of Dundee Ethics Committee. The subjects were in good health on the basis of a physical examination including ECG, biochemistry, haematology, and urinalysis, and were free from all other drug treatment for at least 1 week before the study. They also refrained from alcohol consumption during the 24 h period prior to the study and during the study itself.

Study design

The subjects received two 7-day oral courses of verapamil with a 1-week washout period between treatments, according to a balanced crossover design. The treatments were taken as a series of morning doses of 240 mg sustained-release verapamil. One phase of medication consisted of a whole 240 mg Securon SR tablet for 7 consecutive mornings and the other consisted of the same total dose as the two halves of a tablet of the same formulation for 7 consecutive mornings. The tablets were halved by manually snapping along the score. This procedure produced a clean break in the tablet with no fragmentation. Each subject received two halves from the same tablet ensuring that each dose consisted of 240 mg.

The first dose of each treatment phase was administered under supervision in the Drug Development Unit, Ninewells Hospital. The subjects were then observed for 3–4 h until lunchtime on day 1. A baseline 6-lead ECG was obtained immediately before treatment commenced and at 3–4 h after the first dose of each phase. Subjects returned to the unit at 3–4 h after treatment on day 3 for a further ECG check. Subjects were then admitted to the unit on day 7 of each phase and remained under supervision for the final 24 h of the treatment phase. The final dose was administered after the subjects had fasted overnight and 1 h before the subjects received a light breakfast.

In each phase 10 ml blood samples were obtained immediately before the first dose on day 1, at approximately 3 h post-dose on day 3, and immediately before and at 0·5, 1, 1·5, 2, 2·5, 3, 3·5, 4, 5, 6, 8, 10, 12, 14, 24, 30, and 48 h after the last

dose on day 7. Plasma was separated by centrifugation and stored at –20° prior to determination of plasma verapamil and norverapamil levels by HPLC.[2] The average coefficient of variation of this assay for verapamil and norverapamil over the range 5–400 ng ml^{-1} was 5·5 (range 3·1–8·6) per cent and 4·5 (range 2·7–8·2) per cent, respectively. The limits for reliable quantitation of verapamil and norverapamil were 4 and 2 ng ml^{-1}, respectively.

Pharmacokinetic and statistical analysis

The area under the verapamil and norverapamil plasma concentration versus time curves were determined for one dose interval (0 to 24 h) on day 7 by the trapezoidal rule (AUC_{0-24}). The mean steady-state concentration (C_{mean}) was obtained from the relationship $AUC_{0-24}/24$. Elimination half-lives were calculated by regression analysis of the terminal portion of the log-linear concentration versus time curves using the method of least squares. Plasma profiles were also examined with respect to maximum (C_{max}) and minimum (C_{min}) plasma concentrations over the 24 h dosing period, and time to peak levels of verapamil and norverapamil. Fluctuation in verapamil steady-state levels was calculated using the relationship $(C_{max}-C_{min})/C_{mean}$.

Statistical analysis to examine differences between formulations was carried out using Student's paired *t*-test and Wilcoxon's signed-rank test. In the case of plasma levels the comparisons were carried out using log transformed data. The conclusions arrived at using the non-parametric Wilcoxon's signed-rank test in general support those obtained with the *t*-test and are therefore not reported in detail.

Plasma verapamil and norverapamil levels are expressed as geometric means with 95 per cent confidence limits. All other results are expressed as arithmetic mean ± standard deviation.

RESULTS

Tolerability

A routine ECG recorded on subject 6 3 h after dosage on day 3 of week 1 showed Mobitz type I second degree heart block (Wenckebach phenomenon). This was not associated with any cardiovascular symptoms, although this subject also reported headache. The blood sample taken at this time showed the verapamil and norverapamil concentrations to be 230 and 184 ng ml^{-1} respectively. As a result of these ECG findings, this subject did not proceed further with the study. No other ECG abnormalities were observed during the study: the P–R interval remained within normal limits at all other times in the other 11 subjects.

All subjects showed good compliance with the dosing regimen as judged by the tablet count and plasma drug levels. Tolerability was otherwise excellent.

Pharmacokinetics

Mean plasma verapamil and norverapamil levels are shown plotted ver time in Figures 1 and 2. Since subject 6 was withdrawn from the study on day of the first treatment week the data represent that of 11 subjects. After dos with the whole tablet formulation plasma verapamil levels at 3–4 h on day ranged from 22 to 200 (geometric mean and 95 per cent confidence limits 6 41·6–103) ng ml^{-1}. Dosing with two half tablets resulted in levels of 19 to (67·5, 40·1–113) ng ml^{-1} at the same time on day 3.

Plasma verapamil and norverapamil levels on day 7 varied considerab between subjects throughout the time course studied and this is reflected by lar confidence intervals shown in Figures 1 and 2.

Table 1 shows verapamil pharmacokinetic parameters in individual subjects. The mean peak plasma concentration after the whole tablet, 143 (91·6–223) ng ml^{-1}, was less than that after the two half-tablets, 160 (107–240) ng ml^{-1}, but this difference was not statistically significant (Table 1, p=0·49). There was also no significant difference in the mean time to peak plasma verapamil levels after the two treatments: whole tablets, 3·5 ± 1·2 h, half tablets 3·6 ± 1·0 h (Table 1, p=0·92). The mean trough plasma level was 22·2 (12·6–39·4) ng ml^{-1} after the whole tablet dosing and 22·0 (16·2–29·9) ng ml^{-1} after the half tablets (Table 1, p=0·96). The mean fluctuation in plasma levels expressed as a proportion of the mean steady-state concentration was similar after both treatments: whole tablets, 213 ± 71 per cent, half tablets 218 ± 53 per cent (Table 1, p=0·89).

Comparison of verapamil concentrations at each time point indicated that there was no significant difference between the half and whole tablet (p>0·22). The mean concentration data showed a trend for the levels at 3·5–5 h to be slightly higher after dosing with the half tablet (Figure 1). Mean plasma

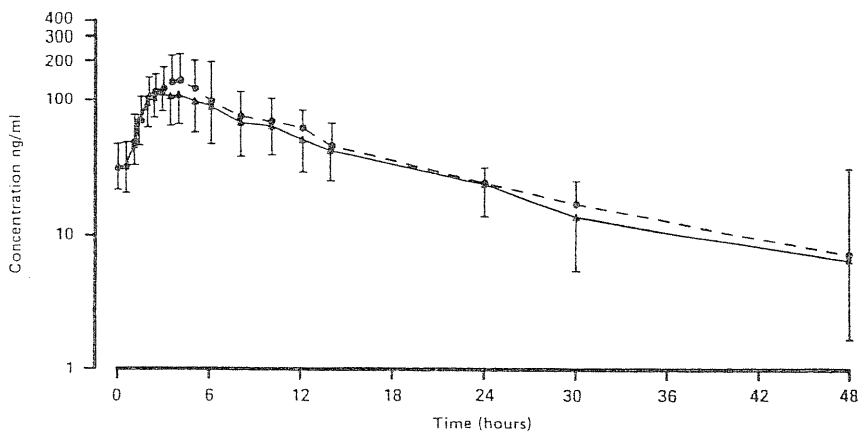

Figure 1. Geometric mean plasma verapamil levels and 95 per cent confidence limits in 11 male volunteers after 7 days once-daily 240 mg verapamil as an intact tablet (Δ) or two half tablets (●)

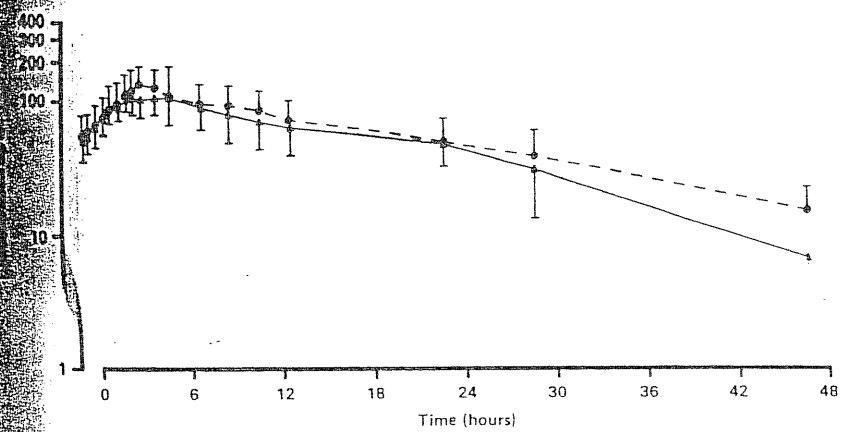

Figure 2. Geometric mean plasma norverapamil levels and 95 per cent confidence limits in 11 male volunteers after 7 days once-daily 240 mg verapamil as an intact tablet (Δ) or two half tablets (●)

verapamil levels at all other times for the two formulations were similar, however, and were virtually superimposable upon one another.

The mean verapamil AUC_{0-24} after the whole tablet, 1733 ± 1125 ng.h ml^{-1}, was not significantly different to that after half-tablet administration, 1780 ± 1057 ng.h ml^{-1} (Table 1, p=0·74). The mean half-life of verapamil after the administration of whole tablets, 10·50 ± 3·35 h, was not significantly different from that after the half-tablet dosage, 9·65 ± 2·26 h (p=0·49).

The findings with respect to dosing with whole versus half tablets which were obtained with norverapamil were essentially similar to those obtained with the parent compound. The levels of norverapamil on day 3 after the whole and half-tablet dosage forms were 28 to 146 (73·7, 53·4–102) ng ml^{-1} and 43 to 273 (77·9, 52·7–115) ng ml^{-1}, respectively. After both treatments the levels of metabolite at the beginning of the dose interval exceeded those of the parent compound. The mean norverapamil/verapamil ratio at zero time of day 7 was 1·75 ± 0·62 (range 0·92–3·34) after whole-tablet dosing and 2·01 ± 0·65 (range 0·45–2·73) after half-tablet dosing. The metabolite/parent drug ratio then declined to reach mean values of 0·83 ± 0·23 and 0·80 ± 0·16 at 1·5–6 h after dosing with whole and half-tablets, respectively.

At no time point were metabolite levels after whole and half-tablet treatment significantly different (p>0·08) although the levels at 3·5–5 h tended to be lower after whole tablet dosing (Figure 2). Peak norverapamil levels after administration of whole tablets, 135 (100–181) ng ml^{-1}, tended to be lower than after half-tablets, 144 (102–203) ng ml^{-1}, but this was not significant (p=0·60). Norverapamil AUC_{0-24} was also similar after administration of the two treatments, 2129 ± 1185 ng.h ml^{-1} after whole tablet and 2245 ± 1214 ng.h ml^{-1} after half-tablet administration (p=0·47). The mean norverapamil half-life after

Table 1. Verapamil minimum (C_{min}), maximum (C_{max}), fluctuation, time to peak (t_{max}), and 0–24 h area under the curve (AUC_{0-24}) after seven single daily doses of 240 mg of sustained release verapamil as whole or half tablets. Geometric means are supplied for C_{min} and C_{max} (with 95 per cent confidence limits) and arithmetic means for fluctuation and AUC (with standard deviation)

Subject	C_{min} ng ml^{-1} Whole	C_{min} ng ml^{-1} Halves	C_{max} ng ml^{-1} Whole	C_{max} ng ml^{-1} Halves	Fluctuation* % Whole	Fluctuation* % Halves	t_{max} (h) Whole	t_{max} (h) Halves	AUC_{0-24} ng.h/ml Whole	AUC_{0-24} ng.h/ml Halves
1	18·2	24·9	251	191	251	220	5	5	2225	1864
2	20·5	25·8	165	98	222	144	6	3·5	1560	1206
3	16·0	10·3	153	86	272	171	2	3·5	1209	1062
4	9·8	23·2	48	150	174	221	2	3	527	1374
5	61·7	31·4	271	305	176	224	3·5	5	2850	2937
7	66·6	46·4	354	529	169	267	4	4	4082	4338
8	26·5	25·5	141	132	186	178	3·5	1·5	1477	1440
9	3·6	18·8	59	87	378	152	3	4	352	1074
10	22·5	15·5	71	158	103	226	3	4	1135	1512
11	60·4	32·7	268	294	184	286	3	3·5	2703	2192
12	21·2	10·9	110	85	227	304	4	2·5	939	584
Mean	22·2 13–39	22·0 16–30	143 92–223	160 107–240	213 ±71	218 ±53	3·5 ±1·2	3·6 ±1·0	1733 ±1125	1780 ±1057

*$(C_{max} - C_{min}) \times 100/C_{mean}$.

whole tablets, 14·76 ± 5·57 h was not significantly different to that after administration of half-tablets 15·43 ± 3·78 h (p=0·75) although with both treatments the half-life of the metabolite was significantly longer than that of the parent compound (p=0·02 and $p<0·001$), respectively.

DISCUSSION

This study describes the plasma level profile of a new sustained-release formulation of verapamil given once daily. Verapamil is well absorbed when given orally and dosing with an aqueous solution results in peak levels within 1 h,[3] after dosing with conventional tablets peak levels are achieved in 1·4–2·4 h.[4] Multiple dosing with a sustained release preparation in the present study resulted in a smooth plasma level curve with peak concentrations occurring between 2 and 6 h. Levels then consistently declined in an apparently monoexponential manner. Plasma half-lives obtained after dosing with sustained release preparations may not provide an accurate estimate of the true elimination half-life since there may be an unknown degree of absorption still occurring during the phase of drug concentration decline. In the present case however concentrations were followed for up to 48 h after the last dose (when absorption would normally have been expected to have ceased) and were not inconsistent with a monoexponential decline. Plasma half-lives were therefore calculated to characterize the profile of the drug for descriptive and comparative purposes.

The mean verapamil elimination half-life in this study, 10·5 ± 3·95 h, is greater than those reported after single oral doses of conventional release verapamil in healthy volunteers, 4·16±0·59h[4] and in patients, 8·2±6·1h.[5] It has previously been shown that verapamil oral clearance is lower after multiple dosing than after a single dose.[5,6] The longer half-life values found in the present study are likely to be the result of a lower clearance associated with chronic dosing.

Plasma levels of the metabolite, norverapamil, and the elimination half-life of this metabolite were greater than those of the parent compound. Schomerus *et al.*[3] found that the half-life for total radioactivity after a single dose of radiolabelled verapamil was 24 h compared with 3 h for the unchanged drug, indicating a much slower rate of elimination for the verapamil metabolites than the parent compound. Kates *et al.*[5] determined verapamil and norverapamil after single dosing with conventional release verapamil and found a longer half-life for the metabolite in two-thirds of the patients examined. Other studies have found similar elimination half-lives for verapamil and norverapamil.[7]

Abnormal ECG findings were obtained in one subject (subject 6) after 3 days treatment with whole Securon SR tablets. This occurred at plasma levels of verapamil and norverapamil which were within the range observed in other subjects and was asymptomatic. No other individuals showed ECG abnorma-

resting vagal tone makes them more susceptible to conduction effects and contrasts with the lesser effects seen in older patients.[8]

The formulation investigated in the present study incorporates verapamil into the hydrocolloid matrix of alginate, a natural polysaccharide, in which the rate of release is controlled by diffusion and surface erosion. The intestinal fluids produce a gel-like diffusion layer through swelling of the alginate. This results in the development of vacuoles and channels which allow a constant rate of diffusion from the gel. This controls the release of verapamil with total release occurring over about 7 h. *In vitro* dissolution studies of water soluble drugs in a different type of formulation (hydroxypropylmethylcellulose) have indicated that with a constant drug/matrix ratio smaller doses have a relatively greater drug dissolution rate.[9] If the same were to happen to the alginate preparation examined in the present study it would therefore be expected that halving the verapamil sustained-release preparation and administering the dose as the two halves could lead to more rapid absorption and higher plasma levels than when the same dose was given as a single tablet. However, the administration of the dose as two half-tablets had little effect on the resulting plasma concentration of verapamil and norverapamil. Absorption of verapamil did appear to be slightly more complete from half than from whole tablets but the magnitude of the differences in t_{max} (3 per cent), C_{max} (12 per cent), C_{min} (1 per cent) and AUC_{0-24} (3 per cent) was small and not significant.

This investigation indicates that the formulation is sufficiently robust to retain its sustained-release properties when the tablet is no longer intact and supports the use of broken tablets as a means of increasing the flexibility of unit dose administration of this sustained-release verapamil.

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Deviation of Tablet Halves from the Ideal Half-Tablet Weights

Drug	Tablet Size and Shape	% of Tablet Halves That Deviated from Ideal Weight by Indicated Percentage			% of Tablet Weight Lost as Powder
		<10%	11–20%	>20%	
Chloroquin	Round, 9-mm diameter	45	29	26	2.4
Daonil	Oval, 10 mm long	97	3	0	0.0
Euglucon	Oval, 10 mm long	87	8	5	0.0
Lasix	Round, 8-mm diameter	45	38	17	2.6
Reglan	Round, 7-mm diameter	33	23	44	2.5

Broken tablets: Does the sum of the parts equal the whole?

Physicians often prescribe doses of medication that necessitate the breaking of tablets into halves. To determine whether halved tablets contain accurate doses, we broke apart 100 tablets each of 5 commonly used drugs: Chloroquin (chloroquine, Indian Drugs and Pharmaceuticals Ltd.); Daonil (glibenclamide, Hoechst Ltd.); Euglucon (glibenclamide, Boehringer-Knoll Ltd.); Lasix (frusemide, Hoechst Ltd.); and Reglan (metoclopramide, CFL Pharmaceuticals Ltd., India). For each of the 5 drugs, 100 intact tablets were weighed individually on an electronic scale. The tablets were then manually broken in half, and each of the resulting pieces was weighed individually. The ideal weight of a tablet half was taken to be half of the mean weight of one whole tablet. The tablet halves were grouped into ranges based on the percentage by which the actual weight deviated from the ideal weight.

The results are shown in the table. The round tablets that were scored on one side only broke unevenly with large deviations in weight. The elongated tablets that were scored deeply on both sides broke cleanly; few halves deviated by more than 10% from the ideal weight. The smallest tablet (Reglan) was most difficult to break accurately. Weight loss from fragmentation and powdering was appreciable for the round tablets but was negligible for the elongated tablets.

To improve the ability of tablets to be broken into halves, we suggest that tablets be elongated in shape, be scored deeply on both sides, and be large enough to permit a firm grip on each end. However, we believe that truly accurate doses can be ensured only if tablets are marketed in all of the strengths used in clinical practice.

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Additional stability guidelines for routinely refrigerated drug products

The recent letter from Sterchele[1] updating stability guidelines for routinely refrigerated products was particularly timely and useful. At the University of Michigan Medical Center, pharmacy personnel are required to label refrigerated medications with the date on which the medications are removed from the refrigerator. This policy was implemented because routinely refrigerated products frequently are dispensed in unit dose medication carts or stored outside of the refrigerator for security reasons (e.g., controlled substances). Nursing and pharmacy personnel were concerned about possible decreased potency if the medications were not used immediately.

Unfortunately, even with the addition of Sterchele's information to previous stability guidelines for routinely refrigerated products,[2-5] we still were lacking room temperature stability data for a number of products. We mailed a questionnaire to the manufacturers of those products and asked them to provide information on the shelf lives of the products at room temperature.

The information supplied by the manufacturers and information that we had on file in the drug information center as a result of previous contact with manufacturers are presented in the table. Some manufacturers who responded to the survey indicated that they had no room temperature stability data or that they would provide information on an incident-by-incident basis. The four caveats reported by Vogenberg and Souney[2] are still applicable and must be considered before using any routinely refrigerated product that has been stored for any period of time at room temperature:

1. Companies cannot accept responsibility for products handled or stored in a manner other than that specified in the package insert,
2. Storage at room temperature for 24 hours may shorten the shelf-life of drugs labeled for refrigeration,
3. Storage at "cool" temperatures does not enhance shelf-life beyond that expected at room temperature, and
4. Solutions, diluents, and reconstituted products should be observed for signs of deterioration (e.g., opalescence or precipitation) before use.

As a result of our survey, we learned that some products previously labeled for refrigeration have been relabeled for storage at room temperature. These products are Cefobid (cefoperazone sodium crystalline powder for injection, Roerig), Amidate (etomidate injection, Abbott), Gammagard (immune globulin i.v. injection, Hyland Therapeutics), Methergine (methylergonovine maleate injection, Sandoz), Pentam 300 (pentamidine isethionate injection, Lypho Med), and Thrombogel (thrombin topical, Johnson & Johnson). Pharmacists should review the labeling of these products prior to removing them from refrigerated storage to ensure that the inventory in stock is labeled for room temperature storage.

Formulation for Clinical Usage "is not intended as a new classification but rather as a means of translation among all systems" and that (p 2133) "The Formulation provides a means for the translation of terminology from one classification to another and for the comparison of clinical therapeutic trials". It is true that some of us[14,15] are not convinced that, in its present form, the formulation can perform these functions, and as far as I know, it has not been used in this way in a clinical trial report. However, despite this categorical statement, there appears to be a widely held but quite erroneous belief, seemingly shared by Krueger, that the Working Formulation is a new diagnostic lymphoma classification approved or devised by the pathologists that served on the study group; it is even said that pathologists at the National Cancer Institute use the formulation "to read slides", a curious habit.

When a clinician sends a lymph node biopsy specimen to a diagnostic pathologist he hopes to receive a brief account of the natural history and prognostic probabilities of his patient's condition, based on the experience of follow-up studies of a wide range of lymphadenopathies over a long period; the pathologist will probably use his own preferred diagnostic term, but he should also, if possible, use the nearest appropriate name from his colleague's favoured classification which he believes he understands. Such advice is not forthcoming from an untried heuristic classification, however excellent its philosophy and immunocytological integration.

It is to be hoped that Krueger's proposals are not a harbinger of a return to the Babel of the 1970s, when Aisenberg wrote "not only do we clinicians have trouble in understanding pathologists, but at times they seem unable to understand one another".[16]

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*This letter has been shown to Professor Krueger, whose reply follows.—ED. L.

SIR,—It was indeed Ockam's razor that prompted us to develop our clinical evaluation scheme. I also agree that the Kiel scheme is excellent for a purely morphological classification. However, its translatability into other classifications, aside from the Lukes-Collins, is limited,[1-3] and this limitation extends to the NCI New Working Formulation which is increasingly used by others (eg, Hoffken et al[4] and in the IARC Multinational Study of Lymphoid Neoplasia), though not by us. Nor do morphologically defined entities always compare with the results of immunological marker studies[5] (the frequency of disparity was 12% in our material). Finally, reproducibility can be a problem in international comparative studies.[3]

In our experience of experimental, comparative, and human lymphoma studies immunological markers are more reliable than morphological criteria for identifying a lymphoid cell exactly. It was thus reasonable to combine Rappaport's original concept of a lymphoma classification with detailed immunocytological data. This provides a simplified morphological categorisation of lymphomas with 6 types, compared with the 24 (and more) morphological entities in the Kiel classification. When we add immunological data, we get 24 (not 42) clearly defined lymphoma entities. This system is also easily reproduced, as shown with Rappaport's original classification.

When immunological marker studies are added to the morphological Kiel classification more than 24 entities will be defined (not to mention discrepancies of a morphological B-cell lymphoma turning out immunologically to be a T-cell or histiocytic tumour).

We do not intend to recommend our simplified classification as a replacement for histological classifications which are well understood by the physician in charge of the patient; rather we offer it as rapid clinical evaluation scheme in cases of difficulty with the language of the diagnostic pathologist. Every current classification scheme can easily be translated into our scheme.

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BREAKING TABLETS IN HALF

SIR,—The primary goal of chronic drug therapy is to find a dose that maximises efficacy and minimises toxicity. To make it easier to tailor doses individually manufacturers often score tablets to assist breaking. Do such tablets really break evenly? To find out, we took one hundred tablets of each of fourteen brands of antihypertensive drug and broke them in two, using the scoring line. We weighed the whole tablet and the two halves separately on precision scales. The theoretical weight of each half was 50% of the whole and we grouped weights as within 5% of expected (45%–55%), 5–10% out in either direction (40–44% or 56–60%), or more than 10% in error (below 40% or above 60%). If at least 95% of the half-tablet weights were within 5% of expected the divisibility of the tablet was classified as "excellent". If 95% or more of the tablet halves were within 10%, divisibility was "moderate". For the remainder divisibility was "poor".

Only two brands ('Lopresor' and 'Logroton') divided well (see table). Most others tested broke easily but deviations in half-tablet weights of up to 10% were frequent, and tablets of 'Tenormin', 'Tenoretic', and 'Aldomet' were unsuitable for breaking, by hand or otherwise. In all cases, the weight loss after breaking was not important.

WEIGHT DEVIATIONS AFTER HALVING TABLETS

Brand	% of tablet halves weighing within:		
	5%	6–10%	10%
Lopresor (metoprolol)	100	0	0
Logroton (metoprolol/chlorthalidone)	100	0	0
Lopirin, Capoten (captopril)	94	6	0
Lasix (frusemide)	91	8	1
Corgard (nadolol)	89	9	2
Moduretic (amiloride/hydrochlorothiazide)	76	21	3
Hygroton (chlorthalidone)	75	24	1
Dilzem (diltiazem)	60	40	0
Visken (pindolol)	59	41	0
Aldomet (methyldopa)	55	37	8
Tenormin (atenolol)	39	41	20
Tenoretic (atenolol/chlorthalidone)	20	43	37

Clearly any assumption that halving a tablet will not lead to inaccurate doses is invalid. This potential source of inaccuracy could be even more significant in clinical situations (our study was done under ideal conditions) and the pharmaceutical industry should tackle it, either by improving divisibility (as already been done for lopresor and logroton) or, even better, by marketing a wider range of unscored tablets to provide all the doses that might be indicated clinically.

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Drug Expenditures
Tablets That Can Be Halved to Save Costs

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Some tablets available by prescription can easily be split in half in order to save the patient money while still providing the optimal dose for his or her medical condition. Tablets that are scored and large enough to allow a firm grip on each end are probably the most conducive to splitting. It is important to consider drugs that have a wide therapeutic window, where the risk for drug toxicity or therapeutic failure is insignificant.

Key words: Cost containment • Drug delivery

For pediatric patients and the elderly, it may be necessary to use half-tablets to provide smaller dosages of a medication than those supplied by the manufacturer. Many oral tablet prescription preparations can be divided without extensively altering their pharmacologic properties, yielding significant cost savings to the patient.

In some situations, tablets are not intended by their manufacturers to be broken in half because of their size, thickness, or design. And many states do not allow the dispensing of split tablets.

However, with medications that are conducive to splitting, the patient can buy an inexpensive "tablet splitter" (usually less than $10), a rigid plastic box with a partition in which a tablet can be placed for splitting. A steel blade affixed to the lid cuts the tablet when the device is closed.[1] While a tablet splitter may be a good alternative for some patients, 1 study found that tablet splitters did not improve the accuracy of dividing tablets into 2 equal parts.[2] If a tablet splitter is going to be used, patients should be instructed about the proper placement of the tablet to avoid cutting themselves when placing or removing a tablet. If a tablet shatters when split or does not consistently break in half when division is attempted, it is surely not a candidate for splitting.

The health care provider and patient may be concerned about the accuracy of tablet splitting and the exact amount of pharmacologically active drug that is obtained; there can be variability in the ideal tablet weight once it is split in half.[2,3] Drugs that have a wide therapeutic window, where the risk for toxicity or therapeutic failure is insignificant, are good options for tablet splitting.

For the most part, tablets that are elongated and deeply scored on both sides are easily split in half. They should also be large enough to permit a firm grip on each end.[3] A patient or provider should avoid splitting, crushing, or manipulating extended-release tablets, such as glipizide (*Glucotrol XL*), as well as those that contain a wax or matrix coating.

Some examples of medications that can be easily split and that lead to cost savings are shown in Figure 1. In this researcher's clinical experience, these examples have led to cost savings, easy tablet splitting, and patient satisfaction. For example, many patients can be treated effectively for depression with sertraline (*Zoloft*) at half the recommended dosage (50mg once daily). Another drug that can be easily split is mirtazapine (*Remeron*); a half tablet (15mg) in the evening can control depression in many individuals.

Valacyclovir (*Valtrex*) 1g tablets, used for the suppression of genital herpes, can easily be split in half to accommodate the recommended daily dose of 500mg.

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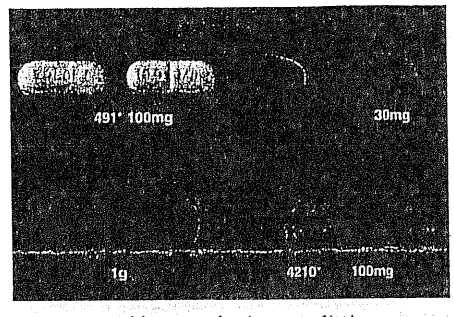

Figure 1. Tablets conducive to splitting. Reprinted from Physicians' Desk Reference, ed 52 (1998; 313,326,330,339), Copyright © 1998, Medical Economics Company.[5]

Fluvoxamine (*Luvox*), used to treat obsessive-compulsive disorder, can be initiated at a dosage of 50mg (half a tablet) daily. However, unless they have liver dysfunction or are sensitive to higher doses because they are elderly, most patients will need a higher dose for maintenance therapy.

At average wholesale price, use of the drugs shown in Figure 1 can lead to a cost decrease of about 50%. For example, if a prescription is written for sertraline 50mg daily, the patient could use number 15 of the 100mg tablets at an average wholesale cost of $34.17.[4] For many patients this cost saving is significant.

Given the ongoing search for drug cost-effectiveness, tablet splitting, in appropriate situations, should be considered. The splitting of certain medications can lead to substantial cost savings. □

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Comparative bio-availability of theophylline whole and halved sustained-release tablets

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Summary

In a randomised, multiple-dose, cross-over study in 14 healthy volunteers, plasma theophylline concentrations were compared during a 12-hour dosing interval after repeated administration of theophylline (Euphyllin Retard; Byk Gulden) as whole and halved tablets. Bio-availability of theophylline from the halved tablets relative to the whole tablets was: 116% (100%, 134%) for the extent of absorption as judged by the area under the concentration time curve (AUC) and 115% (99%, 135%) for the rate of absorption as judged by maximum concentration (C_{max}). The confidence levels for the 80 - 120% bio-equivalence range were 72% (AUC) and 76% (C_{max}), those for the 80 and 125% range were 91% (AUC) and 91% (C_{max}). The plateau times T75% C_{max}, which characterise the sustained-released properties, were 8,5 ± 2,9 hours (halved) and 8,3 ± 2,5 hours (whole) during the 12-hour dosing interval. It is concluded that no clinically relevant deviations in steady-state plasma theophylline concentration and sustained-release properties are likely to result from breaking (halving) the film-coated tablets.

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Theophylline therapy is characterised by great variability in clearance and a narrow therapeutic range.[1,2] In order to facilitate individual dose titration, it has been suggested that some of the commercially available sustained-release tablets can be halved.[3] This is particularly valuable for dosing children on an mg/kg basis. However, before these advantages can be advocated in the labelling of a sustained-release tablet, it has to be shown that halving it does not affect bio-availability.

A study was undertaken to investigate the effects of halving Euphyllin Retard (Byk Gulden) film-coated tablets on the plasma theophylline concentrations under steady-state conditions.

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Subjects and methods

A randomised, multiple-dose cross-over study comprising two treatment periods of 4 days each with a 10-day washout phase was performed on 14 healthy, non-smoking adult male volunteers (mean age 21 years, range 19 - 39 years; body mass 74 kg, range 66 - 86 kg; height 182 cm, range 172 - 188 cm). Before the study, the volunteers underwent physical and clinical laboratory examinations and informed consent was obtained. The study protocol was approved by the University review board.

Subjects were instructed to refrain from taking any medications, including over-the-counter products, for 2 weeks before and during the study. Ingestion of alcoholic and caffeine-containing beverages and foods was not permitted for 72 hours before and during each treatment period.

One theophylline tablet was given 12-hourly at 07h00 and 19h00, respectively, equivalent to anhydrous theophylline 512 mg daily. Tablets were ingested either whole or halved, depending on the randomisation. One film-coated sustained-release tablet contains theophylline monohydrate 281,7 mg and ethylenediamine-dihydrochloride 151,1 mg; this is equivalent to anhydrous theophylline 256 mg. The total daily dose of anhydrous theophylline 512 mg was equivalent to 6,9 (5,9 - 7,8) mg/kg/d (median and range).

On treatment day 4, only the morning dose was given, swallowed with 200 ml of tap water at room temperature. The subjects fasted overnight for at least 10 hours and until 6 hours after ingestion of the drug, when a standardised lunch was served. A standardised snack and dinner were served 9 and 12 hours respectively after the morning dose on day 4. During the first 10 hours after medication, subjects were instructed to drink 200 ml of tap water every 2 hours beginning 2 hours after drug ingestion. Thereafter fluid intake was *ad libitum*.

On treatment day 4, blood samples for determination of theophylline in plasma were drawn before drug intake (0) and at 15, 30, 45, 60 and 75 minutes and 1,5, 2, 2,5, 3, 3,5, 4, 5, 6, 7, 8, 10 and 12 hours after drug administration.

Analytics

Plasma theophylline was assayed on a modular high-performance liquid chromatography (HPLC) system consisting of a Waters autosampler, a Shimadzu pump and a Shimadzu ultraviolet spectrophotometric detector set at 273 nm. Chromatograms were recorded on a Waters integrator. The mobile phase consisted of water : acetonitrile : acetic acid — 92 : 7 : 1 (v/v). The flow rate was 3 ml/min. Separation was achieved in a Waters Radial Pak, Novapak C18, 4 μm, 8 x 100 mm cartridge held in a Waters Z-module compression unit. Proteins in plasma (100 μl) were precipitated by means of acetonitrile (200 μl) containing the internal standard (15 μg paracetamol/ml). After mixing and centrifugation (8 000 *g*) the acetonitrile was evaporated to dryness under nitrogen and the residue redissolved in 160 μl of mobile phase, of which 50 μl was injected. The retention times for paracetamol and theophylline were 3,21 and 4,25 minutes respectively.

Biometrics

Descriptive statistics included mean, standard deviation (SD), standard error of the mean (SEM), median and coefficient of

TABLE II. PEAK-TROUGH CHARACTERISTICS OF THEOPHYLLINE DURING A 12-HOUR DOSE INTERVAL AT STEADY STATE (DAY 4)

Subject No.	% PTF		% swing		% AUC-fluctuation	
	Halved tablet	Whole tablet	Halved tablet	Whole tablet	Halved tablet	Whole tablet
1	29	28	34	33	8	6
2	44	44	59	59	11	11
3	27	49	30	62	8	10
4	36	42	47	61	9	8
5	32	31	38	36	11	7
6	82	32	132	36	16	6
7	25	71	30	125	6	11
8	87	42	142	52	20	13
9	64	40	94	50	16	9
10	54	72	71	104	10	19
11	52	67	74	108	12	15
12	60	73	84	126	17	16
13	25	51	29	74	5	11
14	59	53	89	62	17	7
Mean	48	50	68	71	12	11
SD	21	16	37	32	5	4
% CV	44	32	54	45	42	36

The C_{max} during a 12-hour dose interval at steady state was 7,4 ± 1,5 μg/ml for the halved tablets and 6,5 ± 1,3 μg/ml for the whole tablets. The relative bio-availability was 115% (99%, 135%). As with AUC, this 95% confidence interval was not entirely in the formal bio-equivalence range of 80 - 120%, but this range was covered with a probability of 76%. The range of 80 - 125% was covered with a probability of 91%.

The C_{max} occurred within the first 6 hours after drug intake for both modes of administration. As mentioned (see 'Subjects and methods'), a more suitable characteristic for sustained-release properties is the so-called plateau time. The period during which at least 75% of the observed C_{max} was maintained was 8,5 ± 2,9 h for the halved tablets and 8,3 ± 2,5 h for the whole tablets, the difference not being statistically significant.

The % PTF was 48 ± 21% for the halved tablets and 50 ± 16% for the whole tablets. The % swing was 68 ± 37% for the halved tablets and 71 ± 32% for the whole tablets. Finally, the % AUC-fluctuation was 12 ± 5% for the halved tablets and 11 ± 4% for the whole tablets. The above differences between halved and whole tablets were not statistically significant.

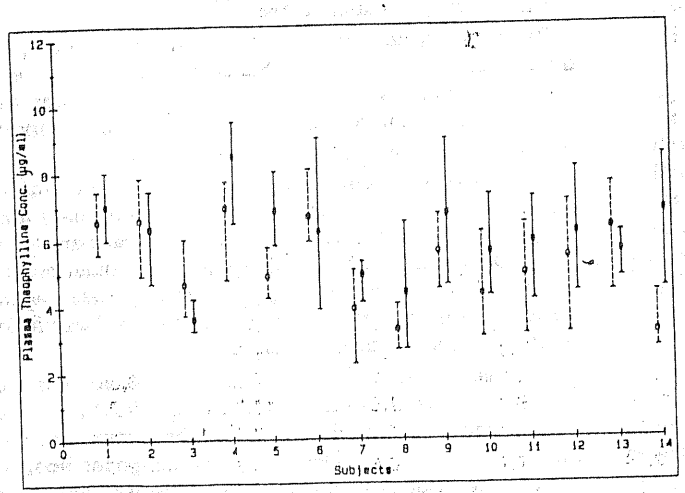

Fig. 2. Individual 12-hour average, peak and trough plasma theophylline concentration during a steady-state dose interval (0 = whole tablet, * = halved tablet) after repeated 12-hourly administration. The average steady-state concentration characterises the extent of absorption; the peak-trough difference characterises the rate of absorption.

The average steady-state concentration as a measure of the extent of absorption and the peak-trough difference as a measure of the rate of absorption are shown in Fig. 2.

Discussion and conclusions

Due to the large interindividual differences in theophylline clearance, individual dose titration is essential for optimum dosing of each patient. Tablets which can be halved are particularly suited to increase or decrease the standard dose by small increments. However, using halved tablets may alter the release pattern and hence the sustained-release characteristic of a particular formulation.[3]

Euphyllin Retard is a film-coated sustained-release tablet which can be halved. The *in vitro* drug release according to a modified paddle dissolution method (half-change test) is almost linear for 14 hours.[8] Previous comparative bio-availability studies under steady-state conditions showed complete bio-availability in comparison with other sustained-release tablets such as Theodur (Draco) and Phyllotemp Retard (Mundipharma).[9,10]

The results obtained show that the administration of halved tablets in comparison with whole tablets yields slightly higher plasma theophylline concentrations. Although conventional bio-equivalence criteria with a 95% confidence level are not satisfied, confidence levels of 72% in the case of AUC and 76% in the case of C_{max} were obtained for the conventional bio-equivalence range of 80 - 120%. When dealing with bio-availability ratios, some authors recommend the use of the 'ratio symmetrical' bio-equivalence range of 80 - 125% instead of the 'difference symmetrical' range of 80 - 120%.[4] The corresponding confidence levels for the range of 80 - 125% are 91% in the case of AUC and also 91% in the case of C_{max}. No clinically significant deviations in steady-state plasma theophylline concentrations are likely to result if the tablets are ingested either whole or broken in half.

Because of the frequency of sampling within the first 4 hours (12 blood samples), differences in T_{max} were observed which have no clinically relevant bearing on the steady-state profiles. The more relevant steady-state characteristic, plateau time T75% C_{max} showed that Euphyllin Retard has good

Table V—Comparison of Absorption Rate Constants (j) between Subcutaneous (sc) and Intramuscular (im) Routes [a]

Compound	j, hr^{-1} sc [b]	j, hr^{-1} im [c]
Sulfamethoxazole	0.78	1.10 ± 0.07
p-Aminoazobenzene	0.14	0.18 ± 0.01
p-Hydroxyazobenzene	0.090 (0.12 ± 0.02) [d]	0.17 ± 0.01
o-Aminoazotoluene	0.040	0.093 ± 0.005
1-Phenylazo-2-naphthylamine	0.0050	0.0093 ± 0.0006

[a] Controlled suspension. C_0, 5 mg/ml; V_0, 0.05 ml. [b] Estimated by extrapolation of data shown in Table IV using Eq. 5. [c] Experimental data (with standard error) cited from the previous report (4). [d] Experimental value (with standard error).

parison using five controlled suspensions. To compare at the same drug concentration (C_0) and injection volume (V_0), the values estimated by extrapolation of the data shown in Table IV using Eq. 5 were used for the absorption rate constants (j) in the subcutaneous route. This comparison shows that the absorption rate from the subcutaneous route is slower than that from the intramuscular route for all the test suspensions. A similar tendency was previously observed for injections of drug-oil solutions (5). The relationship between j and C_0 in the subcutaneous route differed slightly from that in the intramuscular route (Eqs. 9 and 10). Therefore, it should be noted that the difference in j shown in Table V may increase with increasing C_0.

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Dissolution and Bioavailability Studies of Whole and Halved Sustained-Release Theophylline Tablets

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Abstract □ In dissolution studies of whole and halved 100-mg sustained-release theophylline tablets, drug release from halved tablets was significantly higher. These differences were not reflected in the bioavailability studies. The area under the curve (AUC) mean absorption time and fraction-of-dose recovered in urine at 24 hr were not significantly different following the ingestion of whole or halved 100-mg tablets. The elimination rate constant, half-life, volume of distribution, plasma, and renal clearance values were consistent with values reported previously. Discrepancies were found in the 24-hr metabolite distribution as compared to literature values and may be accounted for by the age and health of the subjects and the frequency of dosing.

Keyphrases □ Dissolution—whole and halved sustained-release theophylline tablets □ Sustained-release system—dissolution of whole and halved theophylline tablets □ Bioavailability—whole and halved sustained-release theophylline tablets □ Theophylline—bioavailability and dissolution study of whole and halved sustained-release tablets

Breaking sustained-release theophylline tablets in half is commonly practiced to achieve more accurate milligrams per kilogram dosing in children. The extent to which this affects dissolution and bioavailability is unknown.

In this investigation, 100-mg sustained-release theophylline tablets[1] were used to study the effect of halving tablets on dissolution and bioavailability. No published information about the dissolution of these tablets was available. After oral administration of the 100-mg tablet, however, 90% of the dose was absorbed within 14 hr and almost 100% was absorbed by 28 hr (1). When 300-mg tablets were dissolved, 50% of the dose entered solution by 2 hr and > 90% of the dose entered solution by 6 hr (1).

EXPERIMENTAL

Dissolution—The official USP dissolution apparatus was used (2). Simulated gastric and intestinal fluids were used as dissolution media (2).

Simulated gastric fluid, USP (2), was prepared by dissolving 2 g of sodium chloride and 3.2 g of pepsin in 7 ml of HCl and diluting the solution to 1000 ml with distilled water. This test solution had a pH of 1.2.

Simulated intestinal fluid, USP (2), was prepared by dissolving 6.8 g

[1] Theo-Dur, Astra Pharmaceuticals Canada Ltd., Mississauga, Canada L4X 1M4.

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Table I—Percentage of Theophylline Dissolved of Total from 100-mg Sustained-Release Tablets

Time, hr	Gastric, 100 mg (0.5 tablet)	Gastric, 100 mg	Intestinal, 100 mg (0.5 tablet)	Intestinal, 100 mg
1	33.0 ± 3.2	21.2 ± 3.2	36.3 ± 4.5	29.1 ± 2.3
2	42.1 ± 3.7	29.6 ± 0.9	45.8 ± 7.2	37.2 ± 3.8
3	49.5 ± 4.2	34.0 ± 1.2	52.7 ± 7.4	43.1 ± 4.7
4	54.9 ± 4.3	39.4 ± 1.7	58.5 ± 7.8	47.2 ± 4.9
5	60.4 ± 4.5	43.5 ± 1.5	63.3 ± 8.2	52.3 ± 5.5
6	65.8 ± 4.7	46.1 ± 2.5	66.7 ± 8.6	56.0 ± 6.4
7			70.1 ± 7.2	61.0 ± 6.6
8			73.8 ± 8.5	64.5 ± 6.9
9			76.8 ± 7.6	67.7 ± 7.5
10			78.6 ± 6.5	72.0 ± 7.2
11			82.3 ± 8.4	75.2 ± 8.6
12			84.4 ± 6.7	78.4 ± 7.9
25			91.2 ± 3.5	95.1 ± 7.6

of potassium phosphate (KH_2PO_4) in 250 ml of distilled water. To this solution was added 190 ml of 0.2 *N* sodium hydroxide and 400 ml of distilled water. Ten grams of pancreatin were then added and the resulting solution adjusted to pH 7.5 ± 0.1 with 0.2 *N* sodium hydroxide. This solution was diluted to 1000 ml with distilled water.

The 100-mg sustained-release theophylline tablets, as whole or halved tablets, were tested up to six times in each dissolution medium. The tablet, or tablet halves, were placed in the gold-plated basket and immersed in 900 ml of dissolution medium at 37° in the dissolution apparatus. The basket was rotated at 100 ± 5 rpm. Samples were withdrawn at 1, 2, 3, 4, 5, and 6 hr in gastric fluid and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 25 hr in intestinal fluid under sink conditions.

Bioavailability—Relative bioavailability studies were carried out in seven normal adult volunteers, four female and three male, on 2 study days, 1 week apart, after informed consent was obtained. Their mean age was 30 ± 7 yr (range: 21–39 yr) and their mean weight was 72 ± 21 kg (range: 54–100 kg). As determined by a comprehensive medical history they were in excellent health, were nonsmokers, and were not taking any medication at the time of the study. All volunteers had normal complete blood counts and normal screening tests for renal and hepatic function.

All subjects refrained from the ingestion of tea, coffee, chocolate, and cola for 48 hr before and during the 2 separate study days. On each study day, after an overnight fast with ingestion of no more than 480 ml of water, a heparin lock was inserted, a control blood sample was withdrawn, and a control urine specimen collected. Each subject received a mean 5.20 ± 0.24 mg/kg (range: 4.9–4.6 mg/kg) dose of theophylline to the nearest whole 100-mg sustained-release tablet. Tablets were administered whole or halved along with 120 ml of water. Subjects were assigned by random choice into Study Group 1 or Study Group 2. Study Group 1 received whole tablets the first week and halved tablets the second week. Study Group 2 received the halved tablets the first week and whole tablets the second week.

Blood samples were withdrawn at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 18, and 24 hr. Serum was separated and frozen along with an aliquot of accurately measured pooled 24-hr urine until analysis for theophylline content could be performed. Subjects ate meals of uniform composition 4 and 8 hr after ingestion of the dose.

Assay Procedure—There are many methods for measuring theophylline concentrations and these have been adequately reviewed (3). Reversed-phase high-pressure liquid chromatography (HPLC) appears to be the method of choice and was used in this study[2]. Although direct injection methods are available for both theophylline (4–7) and its metabolites (8), the chromatograms obtained using these methods were not satisfactory. Since theophylline is bound to plasma proteins (9) some of these methods only measured unbound drug. The procedures developed and used were based on older methods (10) involving extraction.

Theophylline Extraction Procedure—To 50 μl of dissolution medium, urine, or serum in a 10 × 75-mm test tube was added 50 μl of aqueous solution of β-hydroxyethyltheophylline (15 μg/ml) as internal standard. A 25-μl aliquot of 20% trichloroacetic acid was added and the solution was vortexed and centrifuged. The supernate was transferred into a clean 13 × 100-mm test tube. After buffering with 300 μl of 2.5 *M* acetate buffer (pH 6.4) the solution was extracted with 2 ml of chloroform–isopropanol (20:1) by vortexing and centrifugation. The aqueous supernate was aspirated and the organic layer evaporated to dryness using low heat and a stream of dry nitrogen. The sample was redissolved in 50–100 μl of mobile phase and a 25 μl aliquot was injected directly onto the column. Theophylline concentration was calculated from a calibration curve of the peak height ratio of theophylline to the internal standard *versus* concentration.

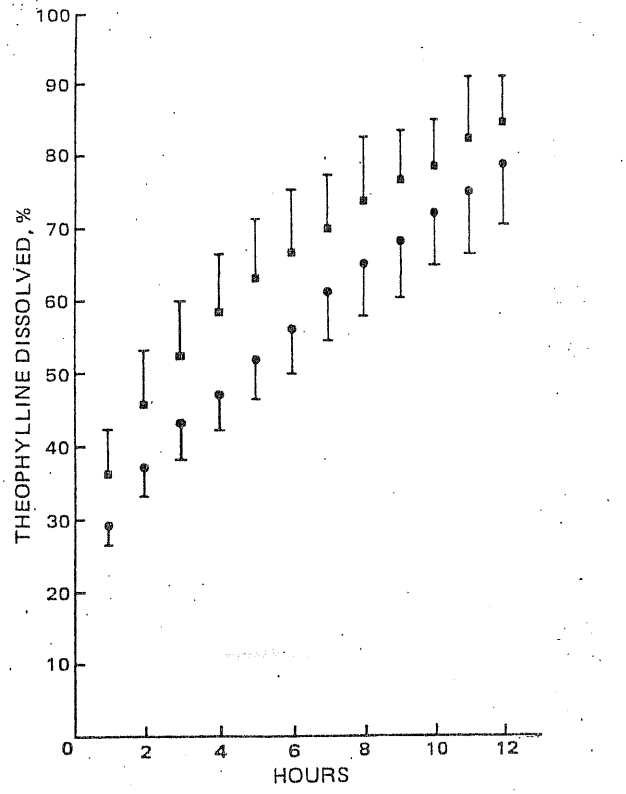

Figure 1—*Percent theophylline dissolved in simulated intestinal fluid* versus *time, from whole, (●) or halved (■) 100-mg sustained-release tablets.*

Theophylline Metabolite Extraction Procedure—To 200 μl of urine, test sample, or standards in solution in urine was added 50 μl of aqueous solution of theobromine (150 μg/ml). After buffering with 150 μl of 2.5 *M* acetate buffer (pH 6.4), the solution was extracted with 4 ml of chloroform–isopropanol (20:1) by vortexing and centrifugation.

The supernate was transferred to a clean test tube with a Pasteur pipet, and 50 μl was diluted with 200 μl filtered, distilled water to yield a final dilution of 1:10 of the urine sample. Exactly 25 μl of the diluted supernate was injected into the HPLC. The concentration of 1-methyluric acid was calculated from a calibration curve in which absolute peak heights *versus* concentration were plotted.

The organic layer from the sample was transferred to a clean, dry test tube and evaporated to dryness in a water bath at 60° with dry nitrogen. The sample was redissolved in 500 μl of mobile phase, and 25 μl was injected onto the chromatograph. The concentrations of 3-methylxanthine and 1,3-dimethyluric acid were calculated from calibration curves constructed by plotting the peak height ratios of the two metabolites to theobromine *versus* concentration of the metabolites.

HPLC Conditions—A 30-cm × 3.9-mm i.d. stainless steel column[3] was used in all assay procedures.

The mobile phase for theophylline was 9% acetonitrile in 0.01 *M* acetate buffer (pH 4.0). At a flow rate of 2 ml/min and an operating pressure of 1500–2000 psi, theophylline and β-hydroxyethyltheophylline had retention times of 4.9 and 6.2 min, respectively.

The mobile phase for 1-methyluric acid was 5% methanol in 0.05 *M* phosphate buffer (pH 4.75). At a flow rate of 2.0 ml/min the 1-methyluric acid had a retention time of 4.0 min.

The mobile phase for the other two theophylline metabolites was 11% methanol in 0.05 *M* phosphate buffer (pH 4.75). At a flow rate of 2 ml/min, 3-methylxanthine, 1,3-dimethyluric acid, and theobromine had retention times of 2.9, 4.2, and 5.1 min, respectively.

[2] The HPLC system consisted of a Model U6K injector, a Model 6000A high-pressure pump, and a Model 440 absorbance detector, all from Waters Associates, Milford, Mass. A 10 mv Omniscribe recorder from Houston Instrument, Austin, Tex. completed the system.

[3] μ Bondapak C_{18}, Waters Associates, Milford, MA 01757

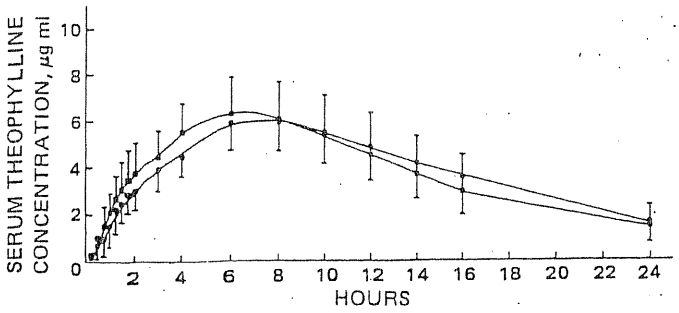

Figure 2—*Mean serum theophylline concentration* versus *time curves from seven normal volunteers who ingested a 5-mg/kg dose as whole (●) or halved (■) 100-mg sustained-release tablets.*

Data Analysis—The theophylline concentration *versus* time curve data from halved and whole 100-mg sustained-release tablets in simulated gastric and intestinal fluid were analyzed by plotting the cumulative percent dissolved *versus* time.

From each of the seven subjects who ingested a mean 5.2 mg/kg dose of theophylline as whole or halved 100-mg tablets, the log serum theophylline concentrations *versus* time curve was plotted. From the terminal linear portion of the curve, the first-order elimination rate constant (K_e) was calculated by:

$$\log Cp = \log Cp_0 - \frac{K_e}{2.303} t \qquad \text{(Eq. 1)}$$

where Cp is the serum theophylline concentration at any time t, and Cp_0 is the extrapolated serum theophylline concentration at zero time, *i.e.*, the y intercept. Elimination half-life values ($t_{1/2}$) were calculated by:

$$t_{1/2} = \frac{0.693}{K_e} \qquad \text{(Eq. 2)}$$

The fraction of the dose absorbed (f) at any time t was calculated by the formula:

$$f = \frac{(Xa)^t}{(Xa)^\infty} = \frac{Cp + K_e \int_0^t Cp\,dt}{K_e \int_0^\infty Cp\,dt} \qquad \text{(Eq. 3)}$$

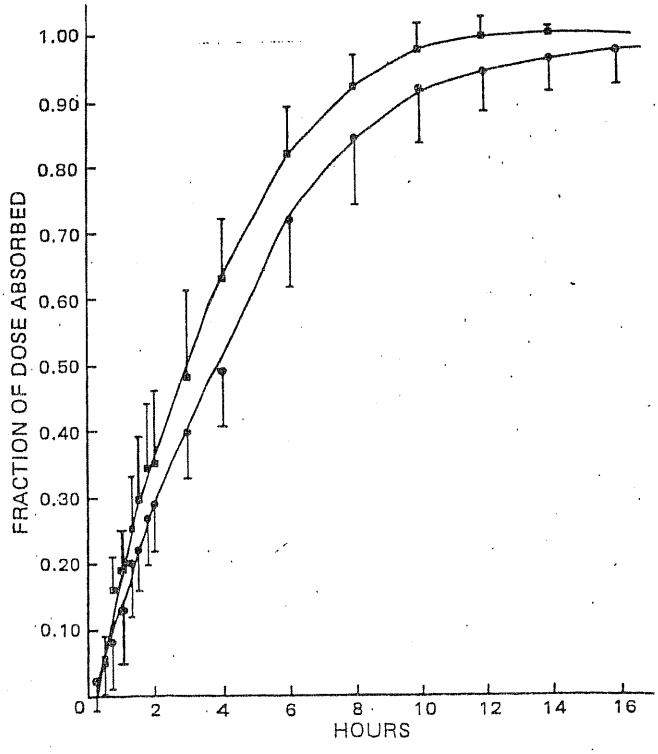

Figure 3—*Mean fractions of a 5-mg/kg dose of theophylline absorbed* versus *time in seven normal volunteers who ingested whole (●) or halved (■) 100-mg sustained-release tablets.*

Table II—Serum Theophylline Concentrations (μg/ml) at Each Sampling Time following the Ingestion of a 5-mg/kg Dose as Whole or Halved 100-mg Sustained-Release Tablets

Subjects	Time, hr 0	0.25	0.5	0.75	1.0	1.25	1.5	1.75	2	3	4	6	8	10	12	14	16	24
Whole Tablets																		
A	—	1.20	1.82	2.21	2.90	3.76	3.66	4.07	4.11	5.26	5.35	7.28	7.17	5.88	5.04	4.09	3.45	1.22
B	—	*tr*[a]	0.42	0.84	1.22	1.85	2.46	3.48	3.72	4.34	5.31	5.21	4.62	3.95	3.27	2.43	1.41	0.36
C	—	—	*tr*	0.90	1.21	1.73	1.87	2.33	2.39	2.81	3.25	4.61	4.03	3.40	2.49	1.76	1.16	*tr*
D	—	0.32	1.34	0.54	0.93	1.61	2.01	2.24	2.53	3.89	4.92	7.48	7.83	7.37	6.34	5.35	4.81	2.37
E	—	*tr*	*tr*	0.04	0.69	1.30	1.76	1.82	1.96	3.13	3.60	5.42	6.59	6.39	5.49	4.61	3.96	1.57
F	—	0.15	1.22	1.77	2.61	3.16	3.19	3.33	3.41	4.35	4.52	5.62	5.79	5.57	5.36	5.00	4.75	3.31
G	—	—	0.02	0.39	0.86	1.57	1.82	2.69	2.88	3.39	4.12	5.14	5.66	6.16	5.94	5.09	4.72	1.71
Mean ± *SD*		0.24 ± 0.12	0.86 ± 0.73	0.96 ± 0.77	1.49 ± 0.89	2.14 ± 0.93	2.40 ± 0.75	2.85 ± 0.80	3.00 ± 0.78	3.88 ± 0.85	4.44 ± 0.82	5.82 ± 1.11	5.96 ± 1.35	5.53 ± 1.40	4.85 ± 1.42	4.05 ± 1.41	3.47 ± 1.57	1.76 ± 1.01
Halved Tablets																		
A	—	*tr*	0.79	2.39	3.06	3.49	4.18	4.86	5.12	6.26	6.88	7.76	7.10	6.13	4.69	3.87	2.94	0.94
B	—	*tr*	0.67	2.02	2.25	2.53	2.91	3.78	3.46	4.49	4.90	5.43	4.52	3.54	2.73	1.70	1.08	0.05
C	—	*tr*	0.92	1.33	1.89	1.80	2.19	2.41	2.54	3.20	3.66	3.74	3.23	2.51	1.32	0.88	0.36	*tr*
D	—	*tr*	0.27	0.79	1.53	2.84	3.49	3.62	3.85	5.41	6.47	8.21	7.85	7.18	5.92	4.75	3.87	1.93
E	—	*tr*	0.54	1.10	1.63	2.30	2.12	2.83	3.15	3.84	5.60	5.92	5.81	5.76	5.10	4.35	3.87	2.10
F	—	*tr*	0.75	2.31	3.17	4.33	4.94	5.12	5.10	5.94	6.67	6.82	6.66	6.15	5.91	4.83	4.31	2.02
G	—	*tr*	*tr*	0.20	0.86	1.21	1.36	1.76	1.40	1.80	4.31	5.85	6.16	6.18	5.46	5.05	4.03	1.65
Mean ± *SD*		—	0.66 ± 0.23	1.45 ± 0.82	2.06 ± 0.84	2.64 ± 1.04	3.03 ± 1.26	3.48 ± 1.24	3.52 ± 1.34	4.42 ± 1.60	5.50 ± 1.25	6.25 ± 1.51	5.90 ± 1.58	5.35 ± 1.67	4.45 ± 1.76	3.63 ± 1.66	2.92 ± 1.58	1.45 ± 0.80

[a] *tr* = Trace: indicates that theophylline was detected but the concentrations were too low to quantitate.

Table III—Fraction (f) of a 5-mg/kg Dose of Theophylline Absorbed at Each Sampling Time following Ingestion of Whole or Halved 100-mg Sustained-Release Tablets

Subject	Time, hr															
	0.25	0.5	0.75	1.0	1.25	1.5	1.75	2	3	4	6	8	10	12	14	16	24
Whole Tablets																	
A	0.10	0.15	0.19	0.25	0.33	0.33	0.37	0.38	0.51	0.57	0.84	0.95	0.97	1.00	1.00	1.02	1.00
B	0.0	0.04	0.07	0.11	0.17	0.23	0.32	0.36	0.47	0.62	0.77	0.87	0.94	0.99	1.01	0.98	1.00
C	0.0	0.0	0.10	0.14	0.21	0.23	0.29	0.31	0.40	0.50	0.79	0.88	0.94	0.94	0.94	0.92	0.94
D	0.03	0.12	0.05	0.08	0.14	0.18	0.20	0.23	0.37	0.49	0.79	0.92	0.99	0.99	0.99	1.01	1.00
E	0.0	0.0	0.0	0.06	0.12	0.17	0.18	0.19	0.32	0.40	0.64	0.86	0.96	0.99	1.00	1.02	1.00
F	0.01	0.10	0.15	0.22	0.28	0.28	0.30	0.31	0.42	0.46	0.62	0.71	0.77	0.82	0.86	0.91	1.00
G	0.0	0.0	0.03	0.07	0.13	0.15	0.23	0.25	0.31	0.40	0.57	0.70	0.84	0.93	0.96	1.01	1.00
Mean ± *SD*	0.02 ± 0.04	0.06 ± 0.06	0.08 ± 0.07	0.13 ± 0.08	0.20 ± 0.08	0.22 ± 0.06	0.27 ± 0.07	0.29 ± 0.07	0.40 ± 0.07	0.49 ± 0.08	0.72 ± 0.10	0.84 ± 0.10	0.92 ± 0.08	0.95 ± 0.06	0.97 ± 0.05	0.98 ± 0.05	
Halved Tablets																	
A	0.0	0.06	0.17	0.23	0.26	0.32	0.38	0.41	0.54	0.65	0.84	0.93	0.98	0.98	1.00	1.00	1.00
B	0.0	0.06	0.18	0.21	0.24	0.28	0.37	0.36	0.51	0.63	0.85	0.94	0.99	1.03	1.02	1.01	1.03
C	0.0	0.11	0.16	0.23	0.23	0.29	0.33	0.36	0.50	0.64	0.83	0.95	1.02	0.99	0.99	0.97	0.98
D	0.0	0.02	0.07	0.13	0.24	0.30	0.31	0.34	0.50	0.63	0.88	0.96	1.02	1.01	1.00	0.99	1.00
E	0.0	0.06	0.12	0.19	0.26	0.25	0.33	0.37	0.48	0.71	0.84	0.92	1.00	1.01	1.00	1.01	1.00
F	0.0	0.07	0.21	0.29	0.40	0.47	0.49	0.50	0.61	0.72	0.83	0.91	0.96	1.03	1.01	1.02	1.00
G	0.0	0.0	0.20	0.08	0.11	0.13	0.17	0.14	0.19	0.44	0.67	0.81	0.92	0.96	1.02	1.01	1.00
Mean ± *SD*	0.0	0.05 ± 0.04	0.16 ± 0.05	0.19 ± 0.07	0.25 ± 0.08	0.29 ± 0.10	0.34 ± 0.10	0.35 ± 0.11	0.48 ± 0.13	0.63 ± 0.09	0.82 ± 0.07	0.92 ± 0.05	0.98 ± 0.04	1.00 ± 0.03	1.01 ± 0.01		

Figure 4—*Mean percentages of a 5-mg/kg dose of theophylline remaining to be absorbed* versus *time in seven normal volunteers who ingested whole (●) or halved (■) 100-mg sustained-release tablets.*

where $\int_0^t Cp\,dt$ and $\int_0^\infty Cp\,dt$ are the areas under the serum concentration *versus* time curves for time 0 to any time t and time 0 to infinity (*i.e.*, total amount absorbed), respectively. The areas $\int_0^t Cp\,dt$ and $\int_0^{t_n} Cp\,dt$ were calculated using the trapezoid method to time t_n. The area $t_n \int_{t_n}^\infty Cp\,dt$ was calculated using Eq. 4 and added to the area $\int_0^{t_n} Cp\,dt$ (11).

$$\int_{t_n}^\infty Cp\,dt = \frac{Cp_n}{K_e} \qquad \text{(Eq. 4)}$$

The mean absorption time (MAT) was calculated by (12):

$$\text{MAT} = \frac{\int_0^\infty Cpt\,dt}{\int_0^\infty Cp\,dt} - \frac{1}{K_e} \qquad \text{(Eq. 5)}$$

Plasma clearance (Cl) of theophylline was given by:

$$Cl = \frac{\text{dose}}{\int_0^\infty Cp\,dt} \qquad \text{(Eq. 6)}$$

where $\int_0^\infty Cp\,dt$ is the area under the serum concentration *versus* time curve for time zero to infinity as calculated in Eq. 3.

The apparent volume of distribution for theophylline (V_d) was calculated from:

$$V_d = \frac{Cl}{K_e} \qquad \text{(Eq. 7)}$$

The renal clearance of theophylline (Cl_R) was calculated by the formula:

$$Cl_R = f_e Cl \qquad \text{(Eq. 8)}$$

where f_e is the fraction of the total amount of the dose in 24 hr urine excreted as theophylline (11).

RESULTS

The mean cumulative percentage of theophylline dissolved from the whole and halved 100-mg sustained-release tablets at each sample time in simulated gastric and intestinal fluids is tabulated in Table I. The mean cumulative percent of theophylline dissolved from the whole and halved 100-mg tablets in intestinal fluid *versus* time is shown in Fig. 1.

Table IV—Theophylline Pharmacokinetics Parameters in Normal Volunteers following the Ingestion of a 5-mg/kg Dose as Whole or Halved 100-mg Sustained-Release Tablets

Subject	AUC, μg/ml/hr	MAT, hr	Elimination Values from Log Plot		Volume of Distribution, (V_d), l/kg	Plasma Clearance (Cl), ml/min/kg	Renal Clearance (Cl_R), ml/min/kg
			K_e, hr^{-1}	$t_{1/2}$, hr			
			Whole Tablets				
A	112.75	3.60	0.11	6.30	0.40	0.74	0.09
B	66.65	4.21	0.18	3.85	0.46	1.36	0.17
C	56.82	4.08	0.16	4.33	0.55	1.47	0.12
D	147.00	4.01	0.08	8.66	0.47	0.63	0.20
E	109.94	5.05	0.10	6.93	0.47	0.79	0.20
F	150.16	5.91	0.03	23.10	1.17	0.58	0.14
G	115.18	6.14	0.11	6.30	0.39	0.71	0.08
Mean ± *SD*	108.36 ± 35.35	4.71 ± 1.00	0.11 ± 0.05	8.50 ± 6.64	0.56 ± 0.27	0.90 ± 0.36	0.14 ± 0.05
			Halved Tablets				
A	109.26	3.37	0.13	5.33	0.35	0.76	0.07
B	59.23	3.86	0.20	3.47	0.46	1.54	0.12
C	39.64	3.35	0.23	3.01	0.55	2.10	0.21
D	136.99	3.29	0.09	7.70	0.45	0.68	0.21
E	128.47	3.44	0.07	9.90	0.58	0.67	0.22
F	139.91	2.64	0.09	7.70	0.42	0.63	0.12
G	111.14	5.28	0.10	6.93	0.44	0.74	0.12
Mean ± *SD*	103.52 ± 39.16	3.60 ± 0.82	0.13 ± 0.06	6.29 ± 2.48	0.46 ± 0.08	1.02 ± 0.57	0.15 ± 0.06

Serum theophylline concentrations from the seven subjects following the administration of a mean theophylline dose of 5.2 mg/kg theophylline as whole or halved 100-mg tablets are listed in Table II. The mean serum theophylline concentration *versus* time plots for the two doses are shown in Fig. 2.

The fractions of the dose of theophylline absorbed (f) at each time interval for each subject following the dose as whole and halved tablets are shown in Table III. The mean values following each dose *versus* time is shown in Fig. 3. The pharmacokinetic parameters, AUC, MAT, K_e, $t_{1/2}$, V_d, Cl_1, and Cl_R for each subject, following both doses, are listed in Table IV. The mean percentage of the dose to be absorbed following the ingestion of whole or halved 100-mg tablets *versus* time is given in Fig. 4. The amounts of the dose recovered in 24 hr in the urine as unchanged theophylline and the various metabolites are shown in Table V. In Table VI the metabolites and theophylline recovery is reported as percentages of theophylline equivalents of the 24-hr urine recovery.

DISCUSSION

The only reference to dissolution data in the literature was from the manufacturer as reported by one group of investigators (1). From the 300-mg sustained-release tablets, 50% of the dose was reported to be in solution by 2 hr and > 90% was in solution by 6 hr. No specifications were reported. In the present study, in gastric fluid, 46.1 ± 2.5 and 65.8 ± 4.7% of the dose was in solution at 6 hr from whole and halved 100-mg tablets, respectively (Table I). The stomach mean emptying time for enteric-coated tablets has been reported to be 3.61 ± 1.47 hr (13); therefore, dissolution studies in gastric fluid were stopped at 6 hr.

In intestinal fluid, 52.7 ± 7.8% of the dose was released in 3 hr by halved 100-mg tablets, and 52.3 ± 5.5% was released in 5 hr by whole 100-mg tablets. After 12 hr, 84.4 ± 6.7% of the dose was in solution from halved tablets and 78.4 ± 7.9% of the dose in 10 hr from whole tablets (Table I). With the paucity of information available in the literature (1), it was not possible to compare previously reported results with the results from the present study.

These sustained-release theophylline tablets are reported to release theophylline by a zero-order rate, *i.e.*, equivalent to an infusion; therefore, plots of percentage released *versus* time should be linear. It was possible to fit a straight line by linear regression ($r = 0.99$) to the terminal portion of the percentage released *versus* time curve. However, the lines did not pass through the origin (Fig. 1). From these data it would appear that the first portion of any dose is probably released by first-order diffusion.

Table V—Fraction of a 5-mg/kg Dose of Theophylline Excreted as Unchanged Drug or Metabolites in 24 hr following the Ingestion of Whole or Halved 100-mg Sustained-Release Tablets by Normal Volunteers

Subject	Theophylline and Metabolites, mg/24 hr				Total Xanthines [a]	Dose	Dose Recovered, %
	1-Methyl-uric Acid	3-Methyl-xanthine	1,3-Dimethyl-uric Acid	Theophylline			
				Whole Tablets			
A	71.28	41.33	193.08	38.34	330.94	500	66.19
B	61.85	36.08	102.72	27.89	228.20	300	76.07
C	64.32	39.46	131.15	19.34	246.44	300	82.15
D	30.56	21.39	52.11	47.36	148.84	300	49.33
E	36.32	23.09	67.26	40.66	163.58	400	40.90
F	50.13	31.72	115.12	64.27	254.13	300	84.71
G	56.08	34.52	204.25	36.76	317.04	500	63.41
							66.11 ± 16.47
				Halved Tablets			
A	70.45	39.20	233.53	32.29	358.75	500	71.75
B	51.89	36.39	187.72	22.30	285.36	300	95.12
C	62.36	37.28	102.38	21.53	218.02	300	72.67
D	43.05	22.75	46.67	48.36	158.78	300	52.93
E	30.05	15.56	44.81	43.87	131.77	400	32.94
F	56.30	33.28	114.16	47.82	244.65	300	81.55
G	44.22	25.33	158.68	41.00	269.23	500	51.55
							65.50 ± 20.97

[a] Calculated as theophylline equivalents on a molar basis.

Table VI—Fraction of the 24-hr Urine Content of a 5-mg/kg Dose of Theophylline Excreted as Unchanged Drug or Metabolites following the Ingestion of Whole or Halved 100-mg Sustained-Release Tablets by Normal Volunteers

Subject	Distribution of Theophylline Metabolites in 24 hr, %			
	1-Methyl-uric Acid	3-Methyl-xanthine	1,3-Dimethyl-uric Acid	Theo-phylline
	Whole Tablets			
A	21.42	13.71	53.29	11.59
B	26.95	15.81	45.01	12.22
C	25.95	17.57	48.62	7.84
D	20.42	15.78	31.99	31.82
E	22.08	15.49	37.57	24.86
F	19.62	13.70	41.39	25.29
G	17.59	11.95	58.86	11.60
Mean ± *SD*	22.00 ± 3.37	14.86 ± 1.85	45.25 ± 9.23	17.89 ± 9.22
	Halved Tablets			
A	19.53	11.99	59.48	9.00
B	18.08	14.00	60.11	7.82
C	28.44	18.77	42.91	9.88
D	26.96	15.66	26.86	30.46
E	22.68	12.96	31.07	33.29
F	22.89	14.93	42.64	19.55
G	17.06	10.79	56.25	15.91
Mean ± *SD*	22.23 ± 4.34	14.16 ± 2.63	45.62 ± 13.51	17.99 ± 10.38

A fraction of each dose in these tablets is contained in uncoated granules. As the tablets do not readily disintegrate, the availability of this portion of the dose by pore diffusion would account for the nonlinear 2–3 hr first-order release of drug. The remaining fraction of the dose is contained in coated pellets. As the tablet begins to disintegrate and the portion of the dose in these pellets is released, the rate of drug availability begins to approximate a zero-order infusion release. This ultimately causes the terminal portion of the curve to approach linearity as shown in Fig. 1. Fractions of the dose released from halved tablets were significantly higher than from whole tablets at all times ($p < 0.05$). This is probably due to the increased surface area exposed by breaking the tablets.

In this bioavailability study in normal subjects of whole and halved 100-mg sustained-release theophylline tablets, relative bioavailability was assessed by comparing the areas (time zero to infinity) under the serum concentration *versus* time curves (*AUC*) (Fig. 2). For halved 100-mg tablets, the *AUC* was 103.52 ± 39.16 μg/ml/hr and for whole tablets 108.36 ± 35.83 μg/ml/hr (Table IV). These were not significantly different ($p = 0.05$). In addition, although the mean serum theophylline concentrations following the ingestion of the halved tablets were numerically higher than the values obtained for the whole tablets up to 8 hr, none of the values were significantly different ($p = 0.05$) (Table II).

The fraction of the dose absorbed at any time (f) was calculated using Eq. 3. All subjects absorbed 50% of the dose from either whole or halved 100-mg sustained-release tablets in the 3–4 hr period (Table III, Fig. 3). Except for subject F, following the ingestion of the whole tablets, all other subjects absorbed 90–100% of the dose in the 8–12 hr period. This is consistent with previous reports (1).

The mean percentage of the dose remaining to be absorbed *versus* time is shown in Fig. 4. The initial portion of the graph is linear. These results can be used to confirm the results of dissolution data that there is apparent zero-order release of theophylline from these tablets. The terminal nonlinear portion of the curve is probably due to the fact that the fraction absorbed calculated using Eq. 3 is approaching the asymptote. Theophylline absorption is rapid and complete once the drug is in solution (14).

The mean absorption times (MAT) calculated from Eq. 5 are shown in Table IV. The average MAT of 3.60 ± 0.82 hr following ingestion of the halved tablet was not significantly different ($p = 0.05$) from the value of 4.71 ± 1.00 hr obtained from the whole tablets. In addition, these values are not significantly different ($p = 0.05$) from previously reported values (15) of 5.67 ± 1.40 and 4.20 ± 1.48 hr following the ingestion of whole and halved 300-mg sustained-release tablets, respectively.

The mean theophylline elimination half-life values in these seven subjects following ingestion of these 100-mg sustained-release tablets were 8.50 ± 6.64 hr for whole tablets and 6.29 ± 2.48 hr for halved tablets. These values are not significantly different ($p = 0.05$) and are comparable to literature values of 3.6–12.8 hr in normal, healthy adults (16). Subject F had an extremely long half-life of 23 hr (Table IV) following ingestion of the whole tablets. This is probably not the true half-life, but a value distorted by continued absorption from the sustained-release dosage form. The half-life in this subject following the halved tablet was 7.70 hr.

The apparent volume of distribution for theophylline following ingestion of whole 100-mg tablets was 0.56 ± 0.27 liter/kg. This was not significantly different ($p = 0.05$) from 0.46 ± 0.08 liter/kg obtained from the halved 100-mg tablets. Both values were comparable to those reported in the literature (16).

Total body clearance of theophylline was found to be 0.90 ± 0.36 and 1.02 ± 0.57 ml/min/kg following ingestion of whole and halved 100-mg sustained-release theophylline tablets, respectively. These clearances were not significantly different ($p = 0.05$) from each other or from values reported in the literature (16). Renal clearance of theophylline has been shown to be dependent upon the urine flow rate (17). However, the values found in this study of 0.14 ± 0.05 and 0.15 ± 0.06 ml/min/kg following the ingestion of whole and halved 100-mg tablets, respectively, were not significantly different ($p = 0.05$) from each other or from values previously reported in the literature (17, 18).

The quantities of theophylline and its metabolites, 1-methyluric acid, 3-methylxanthine, and 1,3-dimethyluric acid, recovered in 24-hr urine following ingestion of ~5-mg/kg dose as whole or halved 100-mg tablets are shown in Table V. The metabolite recovery values were converted to theophylline equivalents and reported along with theophylline as total xanthines. This permitted the calculation of the percentage of the dose recovered in the urine as unchanged drug and metabolites during the 24 hr period. Mean recoveries of 66.11 ± 16.47 and 65.50 ± 20.97% following ingestion of whole and halved tablets, respectively, were not significantly different ($p = 0.05$).

The distribution of the various metabolites following the whole or halved tablet doses (Table VI) were not significantly different ($p = 0.05$). This is not surprising since the other parameters such as *AUC*, MAT, K_e, $t_{1/2}$, V_d, *Cl* and Cl_R were not significantly affected by halving the tablets. However, when compared to other values in the literature, some differences were observed. In a study where 15 older patients were given sustained-release tablets (19), theophylline recovery was 7.7 ± 6.1%, whereas in the present study 17.89 ± 9.27% was found. The recovery of 3-methylxanthine (19) was 36.2 ± 7.3%, while only 14.86 ± 1.85% was recovered in this study. The recoveries of 16.5 ± 3.3% and 39.6 ± 4.5% for 1-methyluric acid and 1,3-dimethyluric acid, respectively (19), were not significantly different ($p = 0.05$) from the present study.

In the previously reported study (19), middle-aged to elderly patients were used, whereas the present study used healthy, young subjects. The older patients were at steady state and 116 ± 36% of the 24-hr dose was recovered in the urine. The younger subjects only received a single dose and only 66.11 ± 47% of the dose was recovered in the 24-hr urine. These differences may account for the discrepancies.

In summary the theophylline elimination parameters such as half-life ($t_{1/2}$), elimination rate constant (K_e), apparent volume of distribution (V_d), clearance (*Cl*), and renal clearance (Cl_R) were not significantly different from literature values obtained in similar subjects. The metabolite excretion pattern differed from that previously reported but the differences in subject age and in the dosage regimen may have accounted for these discrepancies. In conclusion, halving the sustained-release 100-mg theophylline tablets to achieve more accurate mg/kg doses should not affect drug therapy in patients.

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Determination of Related Compounds in Aspirin by Liquid Chromatography

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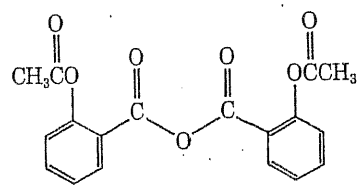
Abstract □ A rapid liquid chromatographic procedure has been validated for the determination of salicylic acid, salsalate, acetylsalicylsalicylic acid, and acetylsalicylic anhydride in aspirin. Samples are dissolved in methylene chloride and analyzed directly by adsorption chromatography in a 7-min separation using an isocratic mobile phase. Recoveries averaged 99% over a 200–10,000 ppm concentration range with standard deviations of <4% for the four compounds of interest. Detection limits ranged from 5 to 36 ppm. Compared to a recently published reversed-phase liquid chromatographic procedure for analyzing aspirin, this method is twice as fast, more sensitive, and avoids the use of hydroxylic solvents which lead to degradation of aspirin and acetylsalicylic anhydride.

Keyphrases □ Aspirin—determination of salicylic acid and related compounds by liquid chromatography □ Liquid chromatography—determination of salicylic acid and related compounds in aspirin □ Salicylic acid—determination in aspirin by liquid chromatography, related compounds

Several recent papers (1–5) have discussed the possible immunological response to the presence of low levels of related compounds in aspirin. Methods, too numerous to discuss, employing gas chromatography, spectrophotometry, liquid chromatography, *etc.*, have been published describing the determination of salicylic acid (I), salsalate (II), acetylsalicylic anhydride (III), and acetylsalicylsalicylic acid (IV) in aspirin. Liquid chromatography (LC) appears to be the most useful approach with respect to specificity, speed, and sensitivity. Various LC methods have appeared in the literature employing adsorption, polar bonded phase, as well as reversed-phase column packings.

After considering the various LC methods, it appeared that the methods employing adsorption chromatography are most appropriate for the determination of related compounds in aspirin on a routine basis. Reversed-phase methods are not desirable because III and aspirin are not stable in the mixed aqueous–organic eluents used in that



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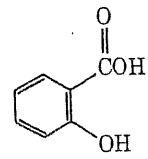

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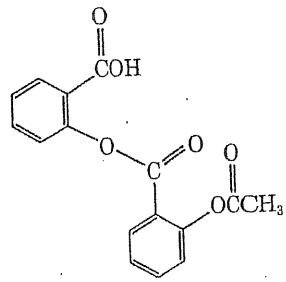

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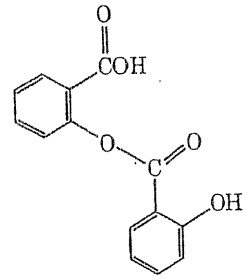

II

form of LC (5). In addition, the selectivity of the reversed-phase system is such that I elutes from the column immediately following aspirin and a poor detection limit is found for I because the larger aspirin peak tails into the peak for I. This difficulty can be avoided by using fluorescence detection (6) to selectively detect I, but this requires the use of dual detectors which increases the cost and complexity of the LC system.

Several normal-phase LC systems have been published for these analyses. A silica gel support containing perchloric acid as a stationary phase for the determination of I, III, and IV in aspirin has been used (7). In another study (8) a polar bonded phase[1] column has been used for the separation of II, III, IV, and other compounds. However,

[1] CYANO.

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taining peak salicylate levels after single dose administration of salsalate capsules.

[a] Computer programs available at the Computer Center, North Dakota State University, Fargo, ND 58105.

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Relative bioavailability and release pattern of whole and halved sustained-release theophylline tablets

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Theo-Dur (Key Pharmaceuticals, Miami, FL 33169) is a sustained-release theophylline tablet which has been shown to be completely and reliably absorbed.[1,2] Theo-Dur is available as 100-mg, 200-mg, and 300-mg scored tablets.

The question as to whether or not Theo-Dur tablets can be broken in half is commonly asked since the tablets are scored and since this flexibility may provide clinicians with the ability to more closely titrate theophylline doses. This study was designed to evaluate the overall bioavailability and pattern of drug release for the halved tablets.

Methods. Six healthy men, aged 24–30 years, who were within 20% of their ideal body weight, served as study subjects. All subjects were nonsmokers and received no medications other than Theo-Dur during the study period. Informed consent was obtained from each subject. Baseline and post-investigation liver function studies, renal function studies, electrolytes, and complete blood count results were all within normal limits for each subject.

Theo-Dur 100-mg, 200-mg, and 300-mg tablets were studied in doses of 600 mg. Subjects received two 300-mg tablets, three 200-mg tablets, and six 100-mg tablets as whole tablets and as tablets broken in half on randomly assigned days. The doses were administered with 240 ml of water.

Aminophylline injection 375 mg was administered orally with 60 ml of orange juice followed by 240 ml of water on the first study day and served as the bioavailability reference.[2] Subjects fasted from midnight of the night before each dose until two hours after the doses were administered. There were at least three drug-free days between study doses.

Blood samples were drawn from the antecubital vein at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours following each dose. The exact collection times were indicated on each sample and were used for final analysis. Theophylline assays were performed by high-performance liquid chromatography using the technique described by Orcutt.[3] The variability produced by repeated analysis of pooled serum spiked with theophylline was less than 5%. Concentrations below 1 mg/liter were not used for analysis.

The areas under the time–serum concentration curves (AUC) for 24 hours were calculated using the trapezoided rule method. The area from the last data point to infinity was estimated by dividing the last data point by the elimination rate constant. The constant used was taken from the elimination curve for the reference aminophylline solution. The constant from the sustained-release tablets was not used because of the possibility of continuing absorption during the elimination phase. The fraction absorbed (FA) was determined by dividing the AUC for the 600-mg Theo-Dur doses by twice the AUC for the 300-mg theophylline reference. We examined the rate of absorption by determining the FA per hour.[4]

Results. The mean FA for all seven treatments was 1.07 ± 0.03 (SEM). The comparison of the fractions

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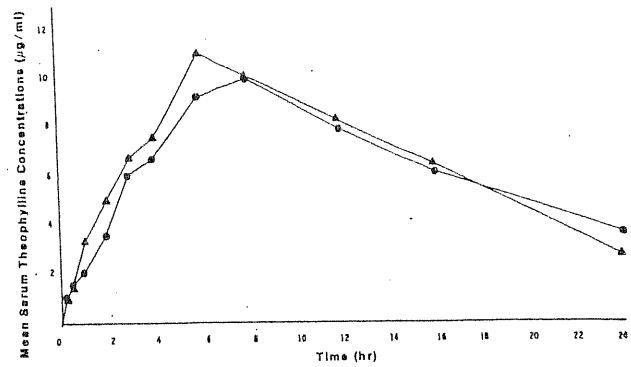
absorbed was found to be not significant ($F = 1.91$ d.f. = 6.30), thus indicating that the bioavailability of Theo-Dur 100-mg, 200-mg, and 300-mg tablets both whole and broken in half is equivalent to the reference aminophylline solution. This supports previously published bioavailability data. Figure 1 depicts representative mean serum theophylline curves for whole and halved tablets. The mean FA/hr curves for 300-mg, 200-mg, and 100-mg whole versus half tablets (ANOVA-randomized factorial design) were compared at each sampling time for the first eight hours of the dosing interval. There were no significant differences in any curve. That is, breaking tablets in half had no significant effect on release characteristics when compared with whole tablets.

Discussion. Fagerstrom[5] simulated serum theophylline concentrations using mean absorption times. In each of two simulations using elimination half-lives of three hours and seven hours, serum levels achieved with half tablets were nearly identical to those achieved with whole tablets. Comparisons made between mean absorption times indicated no statistically significant differences in bioavailability and absorption kinetics. The data presented here support these findings. When the FA per hour for whole and halved tablets were compared, no statistically significant differences in absorption kinetics were found.

Conclusion: Theo-Dur tablets are reliably absorbed, exhibiting complete relative bioavailability. Clinicians may, therefore, take advantage of the flexibility afforded them with scored tablets. Dosage changes as small as 50 mg may be made without fear of altering absorption characteristics while maintaining the convenience of twice daily dosing.

Figure 1. Mean serum theophylline levels for six subjects who received 200-mg whole or halved tablets (• = Theo-Dur whole tablets; ▲ = Theo-Dur halved tablets).



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Letters to the Editor

Mean Dose After Splitting Sertraline Tablets

Sir: Some pharmaceutical companies price all strengths of a particular medication the same. Medications may also be priced so that 1 larger tablet is less expensive than 2 tablets equaling the same dose. Many tablets are scored for breaking or are easy to cut using commercially available tablet cutters.

The Department of Veterans Affairs Medical Centers (VAMCs) and managed care organizations use tablet splitting as a cost-containment measure. For example, a prescription for 10 mg of simvastatin is filled with 20-mg tablets and a pill cutter. Lisinopril, citalopram, metoprolol, and sertraline are medications that are commonly split. If a patient is unable to split tablets, then they are not required to do so.

Concern has been raised regarding the accuracy of the delivered dose of the antidepressant sertraline after splitting the tablets. Since this is one of the medications routinely split, we wanted to determine if tablet splitting caused wide fluctuations in the daily dose.

Method. A class 1 electronic scale (Precisa Balance; Viscount Intralabs, Inc., Lawrenceville, Ga.) was placed in an isolated room and was protected on 5 sides from air movement that would alter the weight of the tablets. Five people volunteered for this pilot study. The ages of the people who cut and broke the tablets ranged from 32 to 77 years (mean = 54 years), and 3 people had varying degrees of degenerative changes in their hands (e.g., arthritis). Two of the participants (P.R.M., J.B.G.) work for the VAMC, 1 works at another hospital, and the other 2 are volunteers at the VAMC. No one was paid for splitting the tablets, and all received brief verbal training on use of the tablet cutter. Each volunteer cut sixteen 100-mg sertraline tablets (professional samples, lot number 9JP047E, expires May 1, 2001, and 9JP169F, expires Dec. 1, 2001) using a pill cutter (LGS Health Products, South Euclid, Ohio) and quickly broke 16 scored tablets by hand. The number of tablets was determined by the number of professional samples available at that time. Each tablet was weighed and split, and the pieces were individually weighed. Data were entered in a Microsoft Excel 97 worksheet. The actual weight of each 100-mg tablet allowed us to calculate the amount of active drug in each portion of the split tablets due to equal distribution of sertraline throughout the tablet.

Results. When a pill cutter was used, the amount of sertraline in the pieces ranged from 45.3 to 54.9 mg (mean ± SD = 49.70 ± 1.98 mg). Breaking tablets by hand gave a range between 43.4 and 56.1 mg (mean ± SD = 49.74 ± 2.58 mg). The difference between the total weight of the whole tablets and the split tablets was calculated, since small tablet fragments would sometimes be left over after the splitting process. From the 160 tablets split, only 88.6 mg (0.55%) of sertraline was unaccounted for in the weighing process. More sertraline was lost using a pill cutter versus breaking tablets by hand: 49.3 versus 39.3 mg, respectively. No tablet pieces were destroyed or unusable.

Discussion. Sertraline has an elimination half-life of 25 to 26 hours.[1] It is metabolized into the active metabolites desmethylsertraline and *N*-desmethylsertraline, with half-lives between 66 to 80 hours and 62 to 104 hours, respectively.[2] The long half-life of sertraline overlaps the daily doses and acts to minimize potential fluctuations in blood levels due to any variation in the delivered dose. In addition, taking the 2 pieces from 1 tablet on consecutive days would help minimize dosing inconstancies.

Tablet splitting is effective for reducing pharmaceutical costs and has been used successfully in appropriate patients.[3] Counseling on how to use a tablet cutter may decrease dosage variance. Our pilot study illustrates the mean dose achieved when 5 people split 100-mg sertraline tablets to obtain a 50-mg dose.

Sertraline tablets were provided by Pfizer, New York, N.Y.

The authors acknowledge Jodi L. Fortwengler, B.S.Pharm., and Buck and Evelyn Schuler for their help in splitting tablets.

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Lamotrigine in the Treatment of Depersonalization Disorder

Sir: It has been proposed that excitatory amino acids such as glutamate might be relevant to the pathophysiology of depersonalization.[1] For example, subanesthetic doses of ketamine, whose effects might be mediated through increased glutamate release, can induce many of the subjective experiences characteristic of depersonalization.[2] Furthermore, pretreatment with lamotrigine, a drug reported to inhibit glutamate release,[3] has been found to attenuate these effects of ketamine.[4,5] We report here on 6 patients with chronic depersonalization disorder in whom treatment with lamotrigine as an add-on therapy brought about a significant clinical improvement.

Method. Eleven patients meeting criteria for DSM-IV depersonalization disorder and diagnosed by means of a semistructured interview using the Present State Examination (PSE)[6] were given lamotrigine as an adjunct to their ongoing medication. All patients had continuous (as opposed to intermittent) depersonalization ranging from 2 to 15 years and had proved resistant

The Potential of Pill-Splitting to Safely Achieve Cost Savings

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Summary: Pill-splitting as a cost-saving measure can be safely used only when implemented judiciously, adhering to drug- and patient- specific criteria and in the context of physician-patient discussion

Abbreviated Title: Pill-splitting in a managed care plan.

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ABSTRACT

Objectives: To present a methodology for identifying specific medications where pill-splitting is clinically appropriate and cost-saving, present data form a commercial managed care population on current pill-splitting practices, and estimate additional cost-savings from extended use of this strategy.

Study Design: Retrospective pharmacy claims analysis.

Methods: Pharmacy claims data from a commercial managed care health plan covering 19,000 lives and national drug data were used to compile a list of frequently prescribed medications. Excluding medications where packaging, formulation, and potential adverse pharmacological outcomes prohibited splitting, we performed a cost analysis of medications amenable to splitting.

Results: Eleven medications amenable to pill-splitting were identified based on potential cost-savings and clinical appropriateness: clonazepam, doxazosin, atorvastatin, pravastatin, citalopram, sertraline, paroxetine, lisinopril, nefazadone, olanzapine, and sildenafil. For these medications pill-splitting is currently infrequent, accounting for annual savings of $6,200 (or $0.03 per member per month), just 2% of the potential $259,500 (or $1.14 per member per month) that more comprehensive pill-splitting practices could save annually.

Conclusions: Pill-splitting can be cost-saving when implemented judiciously using drug- and patient-specific criteria aimed at clinical safety, but is infrequently used at present.

Key words: cost control; prescriptions, drug; physician's practice patterns; prescribing practices; pill/tablet splitting

INTRODUCTION

In recent years there has been a drastic acceleration in the cost of prescription drugs. Patients, insurers, and provider networks continue to bear the burden of prescription drug costs that have increased nearly 60% since 1991 and tripled since 1980.[1]

To alleviate rising prescription drug costs, physicians and providers have employed various cost-saving strategies, including the use of generic medications, selection of more cost-effective medications, tiered systems of drug co-payments, and formulary restrictions.

One cost-saving strategy that may not have yet reached its potential is pill-splitting. Many prescription drugs are available at increased dosages for the same or similar costs as smaller dosages. By prescribing half as many higher strength pills and splitting them to achieve the desired dosage, patients and prescribers can save as much as 50% on the cost of selected medications. As a cost-saving approach, pill-splitting has great potential. For example, a patient being treated with lisinopril (Zestril), 10 mg, will have annual medication costs of $340. By prescribing half the number of 20mg tablets to be split, medication costs will drop to $180 annually, savings of $160 (47%).[2] Similarly, a recent study focusing on splitting psychotropic medications suggests the potential for annual national savings of $1.4 billion.[3]

Pill-splitting is a well-established medical practice[4], not uncommon in prescribing pediatric[5] or geriatric dosages.[6] However, fears of inaccurate dosing, non-compliance, and physical inability to split tablets have discouraged physicians and patients from adopting this practice. Opponents of pill-splitting have cited unpredictable effects on the stability of the drug, loss of drug due to powdering, creation of uneven doses, lack of physical strength and dexterity, poor eyesight, reduced cognitive ability, and lack of instruction as arguments against pill-splitting.[4] However, prior studies suggest that most patients are able to accurately split pills with

minimal loss of tablet content.[4, 7] With some notable exceptions, the chemical stability of most tablet formulations is not meaningfully altered by pill-splitting.[5] Concerns also have been expressed over patient adherence. There is a fear that prescribing higher dosages that require tablets to be halved will lower adherence: patients may not be willing to take the time to split a pill before taking it or may be unable to split a pill. Objectively, however, one study found that splitting tablets had no effect on adherence. It was further suggested that tablet splitting may increase adherence by reducing the cost barrier to adherence faced by some patients.[8]

Pill-splitting is safer and easier when drug- and patient-specific criteria have been met. Medications should not be considered when packaging and pricing structure do not make splitting cost effective or even possible. Medications where splitting could result in adverse pharmacological outcomes should not be split. This includes medications with enteric coatings, extended release formulations, medications with a narrow therapeutic window, and medications with a short half-life to dosing ratio. The use of pill-splitting devices can make splitting tablets easier for patients and often yields more accurate doses[9], while some physical properties of medications such as scoring, shape, and size affect the ease and accuracy of splitting.[7]

Patients should be instructed by pharmacists on how to accurately split tablets or in the use a pill-splitting device. In most cases, patients should be comfortable with splitting their own medication, and they should be free from physical impairments, including poor eyesight, loss of a limb, tremors, debilitating arthritis, or any other condition that might hinder accurate pill-splitting. Pill-splitting by pharmacists may still be a viable option for impaired patients in selected states.[4] While consideration of these many factors suggests that pill-splitting can be undertaken without compromising patient safety, explicit evaluation of this question has not been undertaken.

Pill-splitting also has the advantages of making newer and more expensive medications available to more people who might not otherwise afford them, allowing physicians to individualize a patient's dosage when the medication is not available in the desired dosage, and offering cost-savings without risking needed services being withheld from patients. Pill splitting in pediatric patients may have specific advantages regarding dosage, but may also require special caution.

Though a recent study suggests that pill-splitting may be frequent in long-term care facilities[6], little is known about actual patterns of tablet splitting, particularly in ambulatory settings. This report will describe a methodology for identifying medications amenable to pill-splitting based on specific criteria and use pharmacy claims data to gauge current pill-splitting practices and the potential for additional cost savings.

METHODS

We investigated pill-splitting within a commercial managed care population of 19,000 covered lives served by primary care physicians affiliated with the Massachusttes Gerneral Hospital (MGH). This population consisted of working age beneficiaries receiving employer-based health insurance in the Boston metropolitan area.

We sought to identify specific medications where pill-splitting is appropriate and cost-saving in 2:1 splitting ratios, determine current patterns of pill-splitting among MGH physicians, estimate the potential cost-savings that would result from pill-splitting, and recommend guidelines for safe pill-splitting prescribing practices.

Pharmacy claims data from 1/1/00 through 8/30/00 were available for managed care members with MGH primary care providers. We compiled a list of the 265 most frequently prescribed proprietary and generic medications, both nationally[2] and within the MGH

population. To determine medications amenable to splitting, we evaluated each medication using cost- and pharmacologic-specific criteria. Included were cost-savings per dosage increase based on the average wholesale price (AWP) and actual costs to the health plan, pharmacokinetic interactions and therapeutic window, packaging, and formulation. Physical properties such as scoring and tablet size also were considered, though were not necessarily determining factors.

Preliminary review of the 265 most frequently prescribed medications allowed us to eliminate 125 medications because pill-splitting was not feasible. Among the most common reasons were that medications were available in only one dosage, that a non-oral administration route was used, that a capsule or other non-splittable form was used, and where tablets were prepackaged. Commonly prescribed medications available in a single dose included fexofenadine (Allegra), oxaprozin (Daypro), raloxifene (Evista), and tramadol (Ultram). Common non-oral medications included corticosteroid and beta-agonist inhalers. Capsule formulations among frequently prescribed drugs include terazosin (Hytrin), fluvastatin (Lescol), valsartan (Diovan), fluoxetine (Prozac), and omeprazole (Prilosec). Oral contraceptives are the most common examples of prepackaged medications.

The remaining 140 medications were evaluated on the basis of potential cost-savings on a per dosage basis. For continued consideration, a medication was required to have cost-savings through splitting that exceeded 25% and $0.40 per dosage ($0.20 for generic medications) based on average wholesale price.[2] Of these 140 medications, 61 were eliminated because splitting offered no or minimal cost-savings. Examples of commonly used medications that were eliminated because of the lack of per dosage cost-savings through pill-splitting included buspirone (BuSpar), metformin (Glucophage), famotidine (Pepcid), and cisapride (Propulsid).

Using the 1999 and 2001 *American Hospital Formulary Service Drug Information* indices[10], the 79 remaining medications were evaluated for potential adverse pharmacological

effects. Each medication was screened on the basis of toxicity, rate of absorption, elimination half-life, and therapeutic window. Nine medications with a potential for adverse consequences from splitting were excluded based on manufacturer warning against pill breakage (e.g., nitroglycerin, Nitrostat), non-proportional combination medications (amoxicillin-clavulanic acid, Augmentin), narrow therapeutic window (e.g., warfarin), or rapid half-life to dosing ratio (e.g., tolterodine (Detrol). The latter criteria refers to medications where the elimination half-life is short enough relative to the dosing frequency to raise potential concerns about flucuations in serum concentrations should splitting be inaccurate. Once daily sertraline, with a half-life of 25-26 hours,[10] is an example of a medication with a substantial pharmacokinetic buffer against inaccurate pill-splitting. Olanzapine was included because splitting is feasible as long as the split tablet is used within a week of splitting.

Twenty-two additional medications with extended release formulations were discarded, as altering these medications' physical properties by splitting could negatively impact their pharmacokenetics. Examples of extended release formulations included felodipine (Plendil), extended-release buproprion (Wellbutrin SR), extended-release nifedipine (Procardia XL, Adalat CC) and isosorbide mononitrate (Imdur).

A detailed cost analysis of the 48 remaining medications using data form the available pharmacy claims records allowed us to determine actual cost, current rates of pill-splitting among MGH physicians, and potential savings from extended use of this strategy. Eliminating those medications with minimal usage in the MGH population, we identified eleven recommended medications where pill-splitting is clinically appropriate and cost-saving. Enalapril (Vasotec), nefazadone (Serzone), mirtazapine (Remeron), zafirlukast (Accolate) and clarithromycin (Biaxin) were examples of medications that could have been cost-saving if they were used more frequently in our system.

To calculate current rates of pill-splitting for these medications we used the following methods: for each daily dose for each medication, we calculated the proportion of prescriptions where 2 to 1 splitting was implied by the number of pills provided and the days of therapy supplied by the prescription. For example, for all patients prescribed lisinopril 10 mg per day, we compared the number achieving this dose via 10 mg tablets (30 tablets provided for 30 days) with the number achieving this dose via 20 mg tablets split 2 to 1 (15 tablets provided for 30 days)." For each medication we report the aggregate rate of pill-splitting across all possible 2:1 splitting possibilities. During the time frame we investigated no organizational efforts were in place to promote pill-splitting.

Our cost analysis was based on usage volume and the actual cost of select medications in a commercial HMO population making use of primary care physicians affiliated with MGH. Our unit of analysis was the prescribed daily dose (mg/day) for each of the selected medications, while our outcome measures were the cost-savings realized from halving higher-strength tablets to achieve the desired dosage. To estimate current costs and potential savings we extracted the total number of days of therapy prescribed for each medication at each dosage for all patients as well as the total number of days of therapy for each medication if higher-strength pills were split to achieve the desired dosage. We annualized our 8 months of data to represent expected utilization and costs for a full-year. An annualized cost analysis indicated those medications where sizable current or future cost savings could be expected from pill-splitting.

Observed and potential cost-savings were calculated using the following equations:

Observed annual savings = (savings per day of therapy) x
(# of observed annual days of therapy achieved from pill-splitting)

Potential annual savings = (savings per day of therapy) x (total annual days of therapy)

RESULTS

Top Drugs for Splitting

We identified 11 medications where pill-splitting is clinically appropriate and where significant cost-savings could result (see Table 1). Among these medications there is a preponderance of medications used for psychiatric disorders: clonazepam, citalopram (Celexa), paroxetine (Paxil), nefazadone (Serzone), and sertraline (Zoloft), olanzapine (Zyprexa). Also common were medications for lipid lowering: atorvastatin (Lipitor) and pravastatin (Pravachol) and for hypertension: doxazosin (Cardura) and lisinopril (Zestril). In addition, sildenafil (Viagra), a drug for erectile dysfunction was included.

Of the eleven medications, seven (70%) are scored: clonazepam, doxazosin (Cardura), citalopram (Celexa) paroxetine (Paxil), nefazadone (Serzone), lisinopril (Zestril), and sertraline (Zoloft). The potential average cost-savings from splitting are 36%. Cost savings range from 18% for lisinopril (2.5 mg dose) to 50% for doxazosin (1 mg), nefazadone (100 mg), and sildenafil (25 and 50 mg). Seventy-five percent (18 of 24) of the possible prescribed daily dosages for these medications will yield cost savings of at least 40% per pill.

Pill-splitting is Currently Infrequent

While pill-splitting was employed for a sizable number of HMO members, this practice is relatively infrequent. Splitting was most frequent for sertraline at a dose of 50mg per day, where 75 (12%) prescriptions were made from 100mg tablets to be taken one-half per day compared to 616 (88%) receiving one 50 mg tablet once per day. Other medications where splitting currently occurs are citalopram (8%), doxazosin (4%), and paroxetine (2%). Pill-splitting was either negligible or not observed for the other selected medications.

Current and Potential Cost Savings

Among the selected 11 medications, we calculated that current pill-splitting practices save $6,200 on an annualized basis, an equivalent of only $0.03 per member per month. The largest contributor was citalopram ($2,400). Current cost savings, however, represent only 2.4% of the potential savings that could result from pill-splitting among these 11 medications. Full use of tablet splitting for these drugs would generate $259,500 in savings annually (or $1.14 per member per month). The largest potential contributors to cost savings are atorvastatin ($107,200), lisinopril ($42,100), paroxetine ($26,400), citalopram ($25,700), sertraline ($23,200), and pravastatin ($15,300). While these cost savings are not tremendous, substantial saving could be achieved without necessarily compromising quality of care. Because not all patients should be considered for pill-splitting, achievable savings will be less than these projections, although this report does offer a useful gauge of cost-savings using this strategy.

DISCUSSION

Based on specific criteria focused on safety and frequency, we have identified eleven medications in which extended use of pill-splitting could be cost-saving for a commercial HMO plan. Of these, there is a preponderance of medications used to treat psychiatric disorders, hypertension, and hyperlipidemia. The selected medications share relatively wide therapeutic windows, long half-life-to-dosing ratios, and substantial potential for cost-savings. Pill-splitting is currently infrequent among MGH physicians, accounting for only $6,200 in savings annually, just 2.4% of the potential $259,500 that could be saved from extended use of this cost-reduction strategy for the selected medications. This represents overall savings of 36% off the costs of these selected medications.

A recent lawsuit alleging that a mandatory pill-splitting program adopted by one of the nation's largest health maintenance organizations jeopardized patient safety[11] highlights an important point about appropriate pill-splitting: though it can save money, pill-splitting should only be considered in the context of specific patient-physician assessment and discussion. Review of these legal issues suggests that physicians can reduce the liability risks associated with pill-splitting by judiciously limiting pill-splitting to those medications and patients for whom it is medically appropriate and by engaging in a candid discussion of the requirements, costs, and benefits of a pill-splitting regimen.

Pill-splitting can be expected to be relatively safe when drug- and patient-specific criteria have been met. In addition to appropriate dialog between the physician and the patient, the following medication characteristics should be considered in selecting medications for splitting:

- Wide therapeutic windows insure a buffer against potential fluctuations in dosing that could occur because of inaccurate tablet splitting. This includes medications with a relatively large ratio of drug concentrations producing significant undesired effects to those producing desired effects.
- Fluctuations from mis-dosing also can be minimized by medications that have a long half-life relative to the frequency of dosing because steady-state drug levels are less sensitive to potential variation in individual doses.
- Drugs that have enteric coatings or that are formulated as extended release should not be split.
- Drugs that are prepackaged, such as oral contraceptives, should not be split.
- Medications that do not have a pricing structure that makes splitting cost effective should not be considered for splitting.
- Physical properties of medications affect the ease and accuracy of splitting. For example, tablets that are deeply scored or scored on both sides are easier to split than unscored tablets.[7]

Our list of medications incorporated these characteristics, as well as several others that were specific to our setting, including frequency of prescribing and pricing considerations. While other systems may derive somewhat different lists of medications, the foundation for these decisions should always begin with drug characteristics.

Patient specific characteristics also are also vital to consider in tablet splitting. Patients should be willing and able to be instructed by pharmacists on how to accurately split tablets or in the use a pill-splitting device and they should be comfortable with splitting their own medication. Additionally, patients should have no physical or cognitive impairments that could impede accurate pill-splitting or reliable dosing once pills are split. Conditions of possible import might include poor eyesight, loss of a limb, tremors, debilitating arthritis, dementia, and active psychosis. While some states prohibit pharmacists from splitting tablets[4], pill-splitting may still be a viable option for some impaired patients in selected states. For example, regulations controlling pharmacists do not include such a prohibition in Massachusetts, California, Oregon and New York, among other states. Even where legal, however, lack of reimbursement to pharmacies for pill-splitting may constrain the willingness of pharmacists to perform splitting.

The beneficiary of the cost-savings generated by tablet splitting will vary depending on the system of reimbursement. Self-pay patients or patients with capped pharmacy benefits will reduce their out-of-pocket expenses by splitting their pills. In other instances physicians or health insurance plans will realize the cost-savings, as was the case with the population that we analyzed. Where patients would not otherwise benefit, it would be ideal if patients could be offered an incentive to use split dosages (e.g., a reduction in their co-payment).

Out of convenience we have used data from a commercial health plan, although data from other types of plans could augment our analysis. For example, information on a Medicare

population would be very appropriate given that elderly patients have greater medication use and experience greater out-of-pocket costs that could be diminished through pill-splitting.

Limitations

Several limitations of our review and analysis should be kept in mind. Our results, from a large academic medical center and its physicians, may not reflect current practices and potential cost-savings in other practice settings. We focused only on medications that are preferred in our managed care plan. This excluded several drugs where significant savings also could be realized in other settings (i.e. lisinopril as Prinivil was included but not Zestril). We focused only on 2:1 splitting ratios, although savings may be significant with other dosing ratios. For example, prescribing 75 mg sertraline from splitting three 50 mg tablets over two days rather than three 25 mg tablets in one day. We recognize that the potential cost-savings as reported here may not be fully achievable, as pill-splitting will not be appropriate for every patient. A number of factors may cause actual savings to fall below those potentially achievable, including patient's unwillingness to accept split-dosing prescriptions, patient inability to split pills (either through self-splitting or through a pharmacist), and lack of familiarity by prescribers. Although we lack information needed to estimate the proportion of patients that fall into these categories, this proportion is likely smaller within a employed population compared to other populations. While many factors suggest that more widespread pill-splitting practices could be adopted without compromising patient safety, it was beyond the scope of this study to evaluate the safety of pill-splitting in our population either currently or for our projections of increased splitting. A long-term consideration may be that consistent and widespread adoption of tablet splitting might result in pharmaceutical pricing strategies that eventually eliminate the advantages of splitting.

More likely, however, is that some segments of the market for pharmaceticals (e.g., managed care or self-pay) may adopt pill-splitting to a greater extent than others.

Implications

Our analysis has indicated that significant cost-savings are possible through tablet-splitting for a set of medications selected using explicit criteria. We recommend that physicians talk with patients, review their medications, work with them to assess whether pill-splitting is a viable option, and to use this strategy when it can be carried out safely. The cost savings from this under-used practice are significant and, if implemented judiciously, they present an opportunity to reduce health care costs without compromising quality.

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ORIGINAL RESEARCH ARTICLE
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Potential Savings from Splitting Newer Antidepressant Medications

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Abstract

Background: The newer antidepressants are among the most commonly prescribed classes of medications. A favourable adverse effect profile and approvals for a wider range of disorders than their predecessors have fostered the growth of these drugs. However, newer antidepressants are appreciably more expensive than older medications, and the annual prescription costs of newer drugs are expected to continue to rise at double-digit rates. The price structuring of these medications is largely independent of their pill strengths, and splitting higher strength pills may reduce the average cost per dose by nearly half. Therefore, various health organisations and consumers have been using pill splitting to reduce prescription costs. Antidepressants are well suited for pill splitting because their therapeutic effects depend upon long-term alterations in neurotransmitters, and small variations in dose are not critical.

Objective: To examine the potential savings for various purchasers – health organisations and consumers – that can be derived from pill splitting of newer antidepressants.

Design and setting: Product review and simulation study in the US healthcare setting.

Methods: All new antidepressants with pill strengths that could be halved and were not in capsular or time-release forms were included. Expenditures for purchasers of these pills were calculated using a variety of factors, such as the level of discounting of official average wholesale costs, average retail costs and the site of prescription dispensing.

Results: Seven antidepressants were included. In 2000, 42% of the pills of these antidepressants were at strengths that permitted splitting. If all eligible prescriptions had utilised split doses, purchasers could have saved over $US1.7 billion. The bulk of the saving ($US1.5 billion) would have been realised by pill splitting of only three medications – sertraline, paroxetine and citalopram.

Discussion and conclusions: The economic rationale for pill splitting of antidepressants is compelling for both health organisations and individual consumers. The literature indicates that when pill-splitters are used or a pharmacy cuts the pills, patients are satisfied and compliance is not reduced. However, pill splitting may be inadvisable for some subgroups of patients with reduced cognition or sensory or motor impairment, or older persons on polypharmacy. Pill splitting can be facilitated by mandating manufacturers to score all tablets, requiring phar-

macists to fill prescriptions for split doses, and giving pharmacists incentives for splitting pills for patients. Finally, large-scale studies should be undertaken to examine the clinical effectiveness of, and financial savings from, pill splitting.

Psychotherapeutic medications, particularly antidepressants, are among the most rapidly growing and most commonly prescribed class of medications. Three of the top 12 name-brand medications in the US are selective serotonin reuptake inhibitors (SSRIs).[1] Between 1985 and 1994, there was a 2-fold increase in the number of visits to all US physicians during which antidepressants were prescribed.[2]

The introduction of new medications has contributed to this dramatic increase in prescriptions for psychotherapeutics. The newer medications have a better adverse effect profile than older medications, and some may be more effective.[3] Moreover, many of the newer antidepressants have been evaluated and approved for a wider range of disorders than their predecessors (e.g. anxiety disorders, social phobia, obsessive-compulsive disorder, posttraumatic stress disorders). Nevertheless, newer medications typically cost considerably more than the older medications, which have lost their patent protection and are available in generic forms. For example, between 1995 and 1999, annual prescription drug costs increased at triple the rate of hospital and physician costs, averaging between 10 and 14% for this period; spending for prescription drugs is predicted to continue to increase at double-digit rates over the next 5 years.[4]

A survey of pricing structures of newer psychotherapeutic medications in North America and Europe indicated that acquisition costs to pharmacists were 1.7 to 2.9 times higher in the US than in other countries.[5] Reinhardt[6] concluded that this price differential occurs because US pharmaceutical companies have high financial costs for research, development and marketing but production costs are relatively low (i.e. only 25% of revenues from drug sales are used for manufacturing).[7] Thus, they can sell their products at lower prices to foreign buyers, who otherwise could not afford them. The high prices of newer psychotropic medications, despite their clinical advantages, have curtailed their availability. Many state Medicaid programmes, managed care companies and community mental health centres have limited the use of these drugs in order to control expenditures.[5] It is estimated that approximately two-fifths of persons with severe mental illness do not receive treatment, and the high cost of medications is thought to be one of the principal reasons for this situation.[8]

Although a variety of political solutions have been proposed to address these price disparities, as an immediate practical solution a wide range of consumers and providers have begun to use pill splitting to reduce their expenditures. For example, health maintenance organisations (HMOs), state Medicaid programmes, the Veterans' Administration and individual patients have been reported to be using pill splitting.[9,10] The cost benefits of pill splitting results from the price structuring of medications, in which pricing is largely independent of strength. For example, in the four leading pharmacy chain stores in the US, a 20mg tablet of paroxetine has an average retail price of $US2.38 whereas a 10mg tablet costs $US2.22 (see table I). Thus, a consumer who requires a 10mg dose of paroxetine can split a 20mg tablet and save $US1.03 per dose, or $US376 per year.

Despite the economic advantages of pill splitting, critics have identified a number of potential concerns. McDevitt and associates[11] found that 41% of split pills deviated from the ideal weight by more than 10% and that 12% of pills deviated by more than 20%. Such differences can be critical with certain heart or thyroid medications. On the other hand, Fawell and colleagues,[12] in a study of 1617 patients who were divided into groups that split and did not split tablets, found that pill splitting did not hinder compliance as measured by pill counting. Moreover, patients reported no difficulties with pill splitting and only 4% thought that it affected their willingness to take medication. Finally, a recent Veterans Administration study of sertraline tablets found that splitting 100mg tablets with a pill-splitter or by hand yielded pieces that averaged 49.78 and 49.7mg, respectively.[13] Only 49mg of sertraline was lost per 100 tablets, which would have essentially no effect on plasma concentrations.

Table I. Potential savings by splitting higher strength antidepressant medications. All prices and expenditures are expressed in $US at 2000 values

Drug	Tablet strength (mg)	No. of pills sold per year (thousands)	Wholesale price ($US) per pill	Wholesale price ($US) if higher strength is split	Cash retail price ($US) per pill	Cash retail price ($US) if higher strength is split	Retail price (third party and Medicaid) ($US) per pill	Retail price (third party and Medicaid) ($US) if higher strength is split	Estimated current expenditures from all sources ($US thousands) without splitting	Estimated current expenditures from all sources ($US thousands) with splitting	Estimated annual savings when pills are split ($US thousands)
Sertraline	25	49 738	1.81	0.95	2.16	1.14	2.04	1.05	101 850	52 996	48 854
	50	459 890	1.90	0.95	2.29	1.15	2.11	1.08	979 758	500 659	479 098
	100	137 109	2.08	1.07	2.22	1.19	2.18	1.14	299 450	156 981	142 469
Paroxetine	20	540 435	2.12	1.17	2.38	1.30	2.28	1.24	1 236 797	674 313	562 484
Nefazodone	50	12 190	1.13	0.55	1.26	0.64	1.16	0.58	14 324	7 167	7 157
	100	92 297	1.09	0.55	1.27	0.65	1.16	0.58	108 528	54 486	54 043
Venlafaxine	25	10 235	0.98	0.52	1.25	0.66	1.10	0.58	11 492	6 072	5 420
	37.5	33 553	1.03	0.55	1.27	0.68	1.13	0.59	38 644	20 316	18 327
	50	6 164	1.05	0.59	1.31	0.72	1.16	0.65	7 318	4 087	3 230
Fluvoxamine	25	5 929	2.16	1.10	2.84	1.54	2.30	1.26	14 167	7 711	6 456
	50	31 836	2.31	1.20	3.08	1.57	2.52	1.32	82 964	43 221	39 743
Mirtazapine	15	62 373	2.18	1.14	2.58	1.29	2.28	1.23	145 130	76 758	68 372
Citalopram	20	299 207	1.82	0.95	2.08	1.09	1.97	1.03	592 953	309 681	283 272
Total											1 718 926

In this article, we focus specifically on the splitting of new antidepressant medications, and examine the potential savings that can be realised by various purchasers of these medications such as individual consumers, HMOs, state Medicaid programmes, federal facilities and non-federal hospitals. Based on the earlier research,[14] we hypothesised that substantial savings would be realised by purchasers of antidepressant medications by splitting these pills.

Methods

We included all new antidepressant medications[1] that were among the Red Book's[15] brand name prescription drugs for 2000 and that had strengths that could be halved. We excluded drugs that were in capsular form (e.g. fluoxetine) or that were sustained release or coated such as extended-release venlafaxine and sustained-release bupropion, although for the latter the exposed area of the pill after splitting is so small that the blood concentrations of the drug would probably not be appreciably altered.

1 'New' antidepressants were defined as all antidepressants under patent protection in 2000.

We examined seven antidepressants that had been on the market for all of 2000 (table I). Manufacturer data indicated that 42% of all of the pills of these antidepressants sold in 2000 were at strengths that permitted pill splitting.[16] Our calculation of drug costs to various purchasers includes a variety of factors, such as discounting of official average wholesale costs and use of third-party reimbursements for which precise data are not always accessible. However, it is possible to make a reasonable estimate of the cost per tablet strength of purchasing antidepressants that illustrates the advantages of pill splitting. First, we divided sites of prescription dispensing into two categories. The first category, where pills are purchased directly or indirectly from manufacturers, included non-federal hospitals, federal facilities, HMOs and clinics. The second category included chain stores, independent pharmacies, food stores, mail order prescription plans, home healthcare agencies and long-term care facilities. Thus, in the first category the purchaser of medications is an organisation, whereas in the second category the purchaser is actually the individual consumer, who may receive the drug through various purchasing mechanisms that deal directly or indirectly with the manufacturer. For the seven antidepressants, the proportion of each antidepressant medication dispensed within the first category ranged from 5 to 15%, and between 85 and 95% were dispensed within the second category.[16]

Next, we determined the cost per tablet strength of medication to the purchasers in each category. At sites in the first category we used the wholesaler's actual invoice cost to the purchaser for each strength of medication.[16] For medications dispensed at sites in the second category, we calculated cost per tablet strength to purchasers for prescriptions that were covered by third-party payments and Medicaid on the basis of 90% of the 'average wholesale price' charges listed for each strength of medication.[17] For prescriptions without third-party payment, we calculated consumer expenditures for each tablet strength on the basis of mean prices listed on the websites of the nation's four leading pharmacy chain stores. The percentage of retail prescriptions without third-party payments ranged from 11 to 14% for the seven antidepressants.[16]

Using these methods, we were able to determine what the cost of each strength of pill would be at the wholesale price, the retail price for third-party payments and the cash retail price (table I). Thus, on the basis of data of how many pills were sold at each of the pricing arrangements,[16] we calculated the overall annual expenditures for these medications with and without pill splitting. The difference represented the amount that could be saved by these purchasers if they used pill splitting.

All prices and expenditures are expressed in $US at 2000 values.

Results

As seen in table I, if all eligible prescriptions were used as split doses, purchasers of these pills would have saved over $US1.7 billion in 2000. If one-half or one-quarter of eligible prescriptions had used split doses, savings of $US860 and $US430 million, respectively, could be achieved. It can be seen that the bulk of the savings ($US1.5 billion) could be realised from pill splitting with just three medications – sertraline, paroxetine and citalopram.

Discussion

Our calculations confirm our hypothesis that pill splitting can substantially reduce purchasing expenditures for antidepressant medications. By splitting all strengths of antidepressant medications that were examined in this paper, overall purchasing expenditures of these medications (including all strengths) could be reduced by as much as 30% annually. Moreover, three of the medications – sertraline, paroxetine and citalopram – account for nearly 90% of the savings that could be realised. Thus, pill splitting can potentially benefit individuals and healthcare organisations. Indeed, the economic rationale for pill splitting is so compelling that it is increasingly popular among HMOs, veterans' hospitals, Medicaid programmes and consumers.[9,10]

A limitation of the study is that we could not determine what percentage of antidepressant medications are currently being split, although we believe it represents a very small proportion of prescriptions; consequently, our estimates may be slightly higher than the actual savings that can be realised.

Although the literature is sparse with respect to patient acceptance and utility of pill splitting, it would seem that when pill-splitters are used or when a pharmacy cuts the pills, patients are satisfied and compliance is not reduced.[12,18] Indeed, compliance may be enhanced because of the reduced price of medications. Carr-Lopez and associates[18] reported that only 6% of their sample indicated that a pill-splitter was not easy to use and that they would not use one even if it could save them money. Nevertheless, these findings must be tempered by the fact that a study using an electronic monitoring system found that patients may overestimate their degree of compliance with antidepressant medications.[19] Sedrati and co-workers[20] concluded that although pill-splitters easily cut all types of tablets, best results were obtained with large tablets, those that were coated, were oblong but not pointed, and had flat edges. In the US, a pill-splitter can be purchased at any pharmacy for under $US4.00.

Furthermore, pill splitting of antidepressants is not for everyone.[14] Poor candidates include persons with reduced dexterity, impaired vision, disorganised thinking and diminished cognition. Older persons, among whom polypharmacy is common, may potentially get confused as to which pills to split.[11] We identified two major impediments to pill splitting.[14] First, many pills are not scored in their higher strengths, and some patients feel uncomfortable and imprecise in dividing such pills, even with a pill-splitter. Secondly, this fear is exacerbated by pharmacists who are often unwilling to fill prescriptions that call for half-doses of unscored medication.

In order to further facilitate pill splitting for the individual consumer, we propose that manufacturers be mandated to score all tablets, that pharmacists be required to fill prescriptions for split doses, regardless of whether pills are scored, and that pharmacists be given economic incentives to split pills for patients. Finally, it would be useful to conduct large-scale controlled studies to examine the financial savings and medical effectiveness of pill splitting of psychotropic medications. Such studies must evaluate effectiveness from the perspectives of two potential beneficiaries of pill splitting: healthcare organisations and individuals.

Conclusions

By splitting the newer antidepressant medications, substantial savings can be realised by purchasers of these drugs. In 2000, pill splitting of newer antidepressants could have yielded a savings of $US1.7 billion in the US; the bulk of the savings ($US1.5 billion) would have been realised by splitting tablets of seraline, paroxetine and citalopram. Although uncontrolled studies have found pill splitting to be well accepted and to not disrupt compliance, controlled studies are needed to determine whether pill splitting affects drug adherence and blood concentrations, and whether certain patients are more likely to have difficulty with pill splitting than others. Pill splitting could be enhanced by scoring all tablets and providing economic incentives to pharmacists to split pills.

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Splitting Antidepressant Medications

More Studies Are Needed To Confirm Clinical Outcomes and Potential Savings

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The paper by Cohen and Cohen[1] raises an issue that causes concern to healthcare providers, health professionals and patients worldwide: the inexorable increase in the cost of medication. A commonsense solution that will have a wide appeal is proposed: since (at least in the case of newer antidepressants in the US) price structuring is independent of pill strengths, splitting higher strength pills for patients who need lower doses can reduce the cost of each dose significantly. However, this approach fails to take into account the multiple interdependent relationships that exist in any complex system of healthcare, which require detailed consideration before this work can be accepted at face value.

As the authors have rightly pointed out, not only have the costs of medicines increased, so has their use, resulting in a rate of increase in expenditure that between 1995 and 1999 was three times greater than that of hospital and physician costs. However, there are reasons for this beyond the avarice of the pharmaceutical industry. It would be unreasonable not to expect that the costs of drug development would be much higher in the 1980s and 1990s than they were in the 1950s and 1960s, when the first clinically useful antidepressants were introduced. This is not merely a consequence of inflation as it affects the economy generally. Development costs have spiralled because research techniques have increased both in number and complexity, the time taken from drug discovery to general availability has increased and regulatory demands have, rightly, become more stringent. In addition, newer antidepressants are more likely to deliver the desired outcomes of treatment than the older drugs:[2] studies have consistently found that the higher acquisition costs of newer drugs are more than offset by savings in other areas,[3] and this has been reflected in their increased use. It is possible that the increased expenditure on newer antidepressants has had an impact on reducing the rate of increase in hospital and physician costs.

The high costs of research and development incurred by the pharmaceutical industry are acknowledged. However, no connection is made between these costs and the price of the end product. In the UK, where the National Health Service is a monopoly customer, the profits of the industry are regulated by a price regulation scheme that takes investment in research and development into account. Clinicians and patients want more effective, better tolerated medicines; the industry has a record of innovation, research and new product development to meet clinical needs, and for this a price has to be paid.

Currently, tablet splitting occurs in only a small proportion of prescriptions. If the practice were to become widespread, the impact on the healthcare 'ecology' could be considerable. The pharmaceutical industry would be unable to ignore an estimated loss in revenue of about 30% on these products. Either savings would have to be made, possibly by reducing investment in research, or responses made in other ways, such as changes in the

finds. But pharmacists in the nation's more prevalent types of healthcare facilities, such as community and county hospitals, have been slower to advance into ambulatory clinical positions.

Results from the 2004 American Society of Health-System Pharmacists (ASHP) Survey of Ambulatory Care Pharmacy Practice in Health Systems, show that 233 of responding organizations Touro University—California in Vallejo, who led the ASHP research effort.

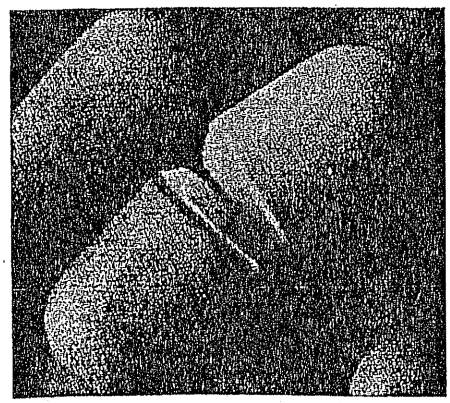
"If you're in a state or organization where your pharmacists are really stretched," said Dr. Knapp, "it's very difficult to take on new activities or expand into new areas when you're having trouble just keeping up with your traditional workload."

see Ambulatory Care, page 21

Tablet Splitting: Half A Solution to Drug Costs

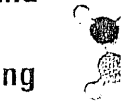
Saving millions, but at a cost to patient care?

NEW ORLEANS—Splitting simvastatin tablets saved $1.26 million in 1999 at a Florida Department of Veterans Affairs (VA) network, with no loss in adherence or clinical outcomes, according to a retrospective analysis presented at the 2004 American Heart Association Scientific Sessions. Full implementation of the simvastatin-splitting initiative across the VA system nationwide avoided costs of $46.5 million in 2003, said lead researcher David Parra, PharmD, Clinical Pharmacist, VA Medical Center, West Palm Beach, Fla.



"[While] exploring ways to accommodate costs ... a number of VA hospitals had the same idea," said Dr. Parra. Simvastatin (Zocor, Merck) was chosen in part because prior research showed that statins could be administered in higher doses every second day and remain as effective as lower daily doses. "Simvastatin also has a very favorable dose-response profile and a good toxicity profile," he added. "If a patient splits a tablet 45/55 instead of 50/50, it won't matter."

see Tablet Splitting, page 16



ORIGINAL RESEARCH

Weight Uniformity of Split Tablets Required by a Veterans Affairs Policy

JAMES E. POLLI, PhD; SHARON KIM, BA; and BRIAN R. MARTIN, PharmD

ABSTRACT

OBJECTIVE: To split several tablet products relevant to the Veterans Affairs (VA) Maryland Healthcare System and assess whether the resulting half tablets provide equal doses.

METHODS: From a VA list of products that are required to be split, 7 products were evaluated, along with 5 other commonly split tablet products. A trained pharmacy student split tablets using a tablet splitter provided by the VA. Half tablets were assessed for weight uniformity.

RESULTS: Of the 12 products subjected to splitting, 8 products (atorvastatin, citalopram, furosemide, glipizide, metoprolol, paroxetine, sertraline, and warfarin) yielded half tablets that passed the weight-uniformity test. The 4 failing products were lisinopril, lovastatin, rofecoxib, and simvastatin. Unusual tablet shape and high tablet hardness predisposed products to failing the weight-uniformity test. The 4 failing products resulted in half tablets that were generally within 20% of their target weight range, suggesting that splitting these specific products would not result in adverse therapeutic effects due to dose variation created by tablet-splitting.

CONCLUSION: Split-tablet results were relatively favorable and generally support a VA practice to split specific tablets. Public quality standards for half tablets, including their content uniformity, are needed to better delineate the policies for acceptable tablet splitting.

KEYWORDS: Tablet splitting, Weight uniformity, Tablet-weight uniformity, Veterans Affairs

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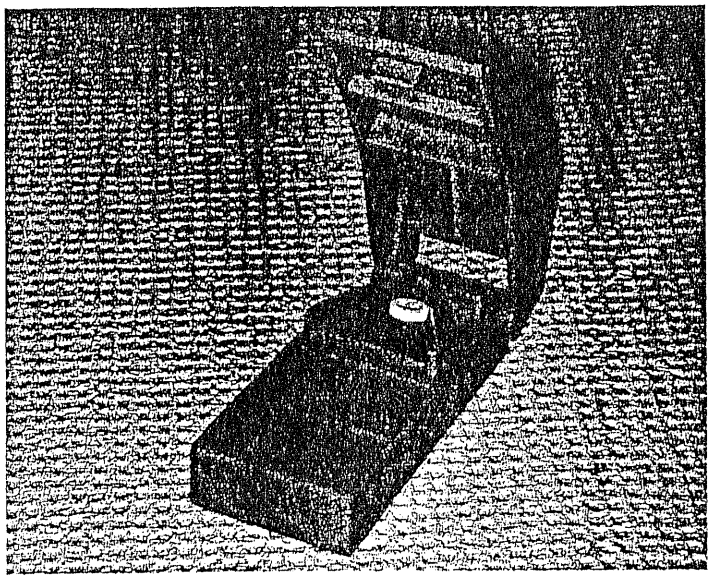
In recent years, the U.S. Department of Veterans Affairs (VA) has been faced with escalating pharmacy costs. These increased costs are the result of increased enrollment, an aging patient population that requires more prescription medicines, and increased acquisition costs of prescription medicines. The VA has turned to tablet-splitting programs as one approach to contain costs. Several pharmacoeconomic studies have indicated that splitting certain tablets can produce significant cost savings.[1-5]

A tablet-splitting program was implemented 2 years ago at the VA Maryland Health Care System, which is part of the Veterans Integrated Service Network 5 (VISN 5) region. VISN 5 provides care for veterans in Maryland; Washington, D.C; eastern West Virginia; Northern Virginia; and south central Pennsylvania.

Candidate drugs were considered for this tablet-splitting initiative if they had a relatively high cost, tablet splitting was not considered to be detrimental to drug release, and the tablets were easily split with a standard tablet-splitting device. VISN 5 now mandates tablet splitting of 8 tablet products for outpatients: atorvastatin, citalopram, lovastatin, paroxetine, rofecoxib, sertraline, sildenafil, and simvastatin. New prescriptions for these products are filled with a tablet that contains twice the prescribed dose, and patients are instructed to take 1 half tablet. A standard tablet-splitting device is also dispensed with the prescriptions. A patient may opt out of the tablet-splitting program if the splitting of tablets proves to be difficult. Also, several other tablets are frequently split, due to cost and therapeutic reasons. Between May 2001 and April 2002, the tablet-splitting initiative directly saved the VA Maryland Healthcare System about $560,000; approximately 41,000 patients received pharmacy services from the health care system during this time.

Equal splitting is presumably necessary for weight uniformity from half tablet to half tablet. We previously found that several commonly split tablets, when split by a razor blade or by hand, usually did not produce evenly split tablet halves.[6] We observed that no visible tablet features (e.g., tablet scoring) predisposed a product's half tablets from passing or failing the uniformity test. Rosenberg et al. found tablet splitting to yield half tablets that generally did not meet an expectation for dose uniformity.[7] They determined the weights and weight uniformity of tablet halves dispensed by pharmacists. Rosenberg et al. found that only 7 of the 22 dispensed prescriptions met an expectation of accurate tablet halves (defined as less than 15% error) with acceptable weight uniformity (i.e., less than 6% relative standard deviation).

FIGURE 1 Photograph of Tablet Splitter



From these recent studies, we hypothesized that tablet splitting following practices of the VA Maryland Health Care System would result in half tablets that generally fail to provide acceptable dose uniformity. Specifically, the objective of our study was to split several tablet products relevant to the VA Maryland Healthcare System and assess whether the resulting half tablets provided equal weights. Seven of the 8 mandatory split products in the VISN 5 region (all but sildenafil) were evaluated, along with furosemide, glipizide, lisinopril, metoprolol, and warfarin, which are commonly split at the VA Maryland Healthcare System. Although not mandatory, splitting of these latter 5 products is permissible, at the discretion of the prescriber. Splitting tablets allows for more precise dosage adjustment and greater patient convenience, for example, by eliminating the need for 2 separate prescriptions to achieve a desired dose. For instance, a patient prescribed lisinopril 30 mg daily can take a 20 mg and a 10 mg tablet, which would require 2 copayments since a 30 mg tablet is not commercially available. Alternatively, the patient could be prescribed one and one-half 20 mg tablets daily, which requires only 1 prescription and only 1 copayment.

Methods

The following products were donated by either the VA Maryland Healthcare System or the University of Maryland School of Pharmacy: atorvastatin 40 mg (Lipitor, Pfizer, Lot #053X0V), citalopram 40 mg (Celexa, Forest, Lot #M0114M), furosemide 40 mg (Geneva, Lot #114028), glipizide 10 mg (Geneva, Lot #126255), lisinopril 40mg (Prinivil, Merck, Lot #L4686; generic lisinopril was not available at the time of this study but is now purchased by the VA), lovastatin 40 mg (Mevacor, Merck, Lot #L1143; generic lovastatin was not available at the time of this study but is now purchased by the VA), metoprolol tartrate 50 mg (Caraco, Lot #1333A), paroxetine (Paxil, GlaxoSmithKline, Lot #400019B13), rofecoxib 25 mg (Vioxx, Merck, Lot #L3103), sertraline 100 mg (Zoloft, Pfizer, Lot #9JP018A), simvastatin 20 mg (Zocor, Merck, Lot #L1016), and warfarin 5 mg (Coumadin, DuPont Pharmaceuticals, Lot #SP094A).

The previously described tablet-splitting method and acceptance criteria were followed,[6] with the exception that a tablet splitter (ACE-LIFE Pill Splitter model PS12E; Health Enterprises Inc., North Attleboro, MA) was used. This tablet splitter consists of upper and lower platforms, which are connected by a hinge. The lower platform provides for the placement of the tablet within a V-shaped region. A razor blade is centered on the upper platform. A tablet is split by pressing the upper platform onto the lower platform (Figure 1). This model of tablet splitter is distributed to VA patients who are instructed to split tablets. For this study, one trained, supervised pharmacy student (tester) performed all tablet splitting in a controlled laboratory environment. This study design did not employ patients; rather, it employed a trained tester to split tablets, since individual patients are known to vary in their ability to split tablets. In evaluating the hypothesis that tablet splitting would result in half tablets that generally fail to provide acceptable dose uniformity, our methodology represents a best-case approach.

Each tablet was carefully placed in the designed split area of the splitter; in all cases, the aim was to obtain evenly split tablet halves. The tester split Zestril 40 mg tablets to affirm the ability of the tester to obtain the favorable tablet-splitting results reported previously (i.e., weight uniformity that passes the acceptance criteria).[6] If a tablet was scored, the tablet was situated in the splitter such that the blade would cut within the score groove. However, for warfarin and furosemide, splits were also performed when the tablet was randomly placed in the splitter (i.e., random orientation of the tablet score relative to the blade). Also, because of its trapezoid shape, lisinopril (Prinivil) could be placed into the splitter with 2 different orientations; both orientations were evaluated.

The previously applied criteria were followed in assessing whether the resulting half tablets split uniformly.[6] The criteria were adapted from the U.S. Pharmacopeia's (USP) <905> "Uniformity of Dosage Units" test for whole tablets.[8] Briefly, the test entailed subjecting 30 tablets of each product to the following:

- 30 tablets were weighed. The mean weight per tablet was calculated. The acceptable 85% to 115% range for a perfectly split tablet was determined from this mean weight. All weight measures employed a Mettler AE 100 analytical balance (Mettler Toledo, Inc., Columbus, OH).
- 10 of the 30 tablets were individually weighed. Each tablet was split, resulting in 20 half tablets. Each half tablet was weighed.
- From the 20 half tablets, the number of tablet halves outside the 85% to 115% range was counted. The number outside the 75% to 125% range was also counted. The relative standard

TABLE 1 Performance of Tablets That Split Successfully

Product	Percent Outliers Beyond 85%-115% (and Beyond 75%-125%)	Percent RSD	Percent Dose Loss (≤ Max)	Observations	Scored (Y/N)	Flat (Y/N)	Tablet Shape
Celexa 40 mg	0 (0)	6.1	0.2 (0.4)	Dramatic score; appears to facilitate accurate splitting	Yes	No	Oval
Coumadin 5 mg (orientation 1)	0 (0)	3.3	0.00 (0.18)	Tablet situated such that blade would split tablet along the score	Yes	No	Round
Coumadin 5 mg (orientation 2)	0 (0)	6.2	0.5 (1.4)	Tablet situated such that score was randomly oriented relative to blade	Yes	No	Round
Furosemide 40 mg (orientation 1)	0 (0)	3.9	0.8 (1.7)	Tablet situated such that blade would split tablet along the score	Yes	Yes	Round
Furosemide 40 mg (orientation 2)	0 (0)	7.8	1.3 (7.3)	Tablet situated such that score was randomly oriented relative to blade	Yes	Yes	Round
Glipizide 10 mg	0 (0)	6.1	0.08 (0.95)	Tablet situated such that blade would split tablet along the score	Yes	No	Round
Lipitor 40 mg	0 (0)	5.5	0.1 (0.4)	Tablet situated such that blade would split tablet where a score would be; difficult to position in the splitter	No	No	Oval
Metoprolol 50 mg	0 (0)	5.4	0.1 (0.4)	Tablet situated such that blade would split tablet along the score but the most difficult to position in the splitter since the tablet is oblong	Yes	No	Oblong
Paxil 40 mg	0 (0)	3.5	0.56 (1.00)	Tablet situated such that blade would split tablet where a score would be	No	No	Oval
Zoloft 100 mg	0 (0)	3.3	0.1 (0.3)	Tablet situated such that blade would split tablet along the score	Yes	No	Oblong

deviation (RSD) of the half-tablet weights was calculated. If, at most, 1 half tablet was outside the 85% to 115% range, but within the 75% to 125% range, and if the RSD was ≤10.0%, the half tablets passed this uniformity test.

- If 2 half tablets were outside the 85% to 115% range (but within 75% to 125% range) or if RSD >10.0%, the additional 20 tablets were split. To pass, none of the additional 40 half tablets could be outside the 85% to 115% range, and the RSD for all 60 half tablets needed to be ≤10.0%.
- If 3 or more of the 20 half tablets were outside the 85% to 15% range, the half tablets failed this uniform test. Also, if any half tablets were outside the 75% to 125% range, the half tablets failed this uniformity test.

Hence, like the USP "Uniformity of Dosage Units" test for whole tablets, half tablets could fail because of too many half tablets outside the 85% to 115% range, too many half tablets outside the 75% to 125% range, or too high an RSD. However, the criteria applied here are more liberal than the USP test for whole tablets, since the USP test allows an RSD of a maximum 6%. Also, half-tablet weight, rather than chemical assay of actual drug, was evaluated. These 2 aspects facilitate tablet halves to pass the uniformity test. The percent-dose loss due to the splitting process was also monitored. The percent-dose loss was the relative difference between the weight of the original tablet and the combined weight of its 2 half tablets.

Results

Of the 12 products subjected to splitting, 8 products (67%) yielded half tablets that passed the weight uniformity test. These results generally contrast with previous results where 8 of 11 razor-blade-split products provided half tablets that failed.[6] Tables 1 and 2 list the products that passed and failed, respectively. Using a tablet splitter in this study, all 6 scored tablets passed, while most unscored tablets failed (4 of 6 failed). This tendency conflicts with a previous observation that no visible tablet features (e.g., tablet scoring, tablet shape) predisposed a product's half tablets from passing or failing the uniformity test.[6] Among the 3 products included in both our previous and the present study, paroxetine and sertraline each passed in both studies, while atorvastatin failed previously but passed here.

Warfarin and furosemide passed, regardless of how the tablet score was oriented relative to the splitter's blade (Table 1). For each of these products, results from the random orientation were slightly less desirable than the results from the nonrandom orientation. Lisinopril failed, regardless of how the tablet score was oriented relative to the splitter's blade (Table 2).

Rofecoxib and simvastatin (Table 2) failed the uniformity test for every reason: too many half tablets outside the 85% to 115% range, too many half tablets outside the 75% to 125% range, and too high an RSD. Lovastatin and lisinopril in one orientation (i.e., the orientation that provided a more stable fit of the Prinivil tablet within the tablet splitter) failed for 2 of these 3 reasons. Lisinopril in the other orientation (i.e., the orientation that provided a poor fit of the tablet within the tablet splitter) failed for all 3 reasons.

Discussion

Favorable Tablet-Split Results

The objective of this report was to split several tablet products relevant to the VA Maryland Healthcare System and assess

TABLE 2 Performance of Tablets That Did Not Split Successfully

Product	Percent Outliers Beyond 85%-115% (and Beyond 75%-125%)	Percent RSD	Percent Dose Loss (≤ Max)	Observations	Scored (Y/N)	Flat (Y/N)	Tablet Shape
Mevacor 40 mg	15 (0)	10.4	0.9 (3.2)	Failed by a small margin	No	Yes	Octagon; thick
Prinivil 40 mg (orientation 1)	20 (0)	13.4	1.5 (7.2)	This orientation provided a good fit of the tablet within the tablet splitter	No	Yes	Trapezoid (but not a square); top of the tablet was inserted toward the blade of the tablet splitter
Prinivil 40 mg (orientation 2)	40 (10)	15.8	0.6 (1.0)	This orientation provided a poor fit of the tablet within the tablet splitter	No	Yes	Trapezoid (but not a square); bottom corner of the tablet was inserted toward the blade of the tablet splitter
Vioxx 25 mg	50 (20)	21.1	1.9 (6.2)	Thick and hard tablet; most difficult to split since the blade is able to move tablet during splitting	No	No	Round; the tablet is almost spherical, due to its small tablet diameter, round shape, and convex (nonflat) surface
Zocor 20 mg	20 (10)	15.0	0.00 (1.30)	Difficult to position the tablet in the splitter	No	No	Shield-like; the tablet's sharpest point was inserted toward the blade of the tablet splitter

whether the resulting half tablets provided equal doses. Our findings here are surprisingly favorable. Using the same criteria applied here, our previous observations from razor-blade splitting showed that a majority of tablets did not split evenly and visible tablet features did not predict a product's half tablets from passing or failing the uniformity test.[6] Using similar criteria, Rosenberg et al. also observed tablet splitting that resulted in half tablets that generally did not exhibit half-tablet uniformity.[7]

Hence, our expectations for this study were low. However, the results are relatively favorable and generally support the mandatory tablet-split policy of the VISN 5 region. Of the 12 products subjected to splitting, 8 products yielded half tablets that passed the weight-uniformity test. For these 8 products, including warfarin, it would appear that motivated and capable patients, under the direction of a pharmacist, would not experience any adverse therapeutic effects due to dose variation from tablet splitting. This conclusion is based on the half tablets of these 8 products exhibiting weight uniformity to whole tablets.

One possible explanation for the differences between this study, where a majority of tablets passed, and our previous results, where a majority of tablets failed, is that the use of a specific model of tablet splitter provided better tablet splitting. However, Sedrati et al. identified several tablet products that, when split using a tablet splitter, resulted in half tablets with doses outside a 85% to 115% range of the target half-tablet dose.[9] Similarly, Horn et al. found several products used in pediatric patients to not split equally.[10] Another possibility is that the VA was selective in identifying tablet products for splitting (i.e., preferentially selected tablets that split evenly). The VA has previously indicated that sertraline tablets split accurately.[11]

Possible Role of Tablet Shape and Hardness in Less-Favorable Tablet-Split Results

The 4 products that failed the weight-uniformity standard were lovastatin, lisinopril, rofecoxib, and simvastatin. In contrast to our previous observations that scoring, or any other visible characteristic, could not predict uniformity test results,[6] a tablet score here tended to explain whether a tablet passed or failed the uniformity test. However, we suspect that shape and tablet hardness, and not scoring, were perhaps the true determinants of acceptable uniformity. Relative to the products that split evenly (Table 1), 3 of the 4 failed products (Table 2) have unusual shapes. Lisinopril (Prinivil) is trapezoidal in shape, with no central axis that could provide an even split. Additionally, lisinopril, in either orientation, did not sit well within the tablet splitter; the tablet did not match the angle of the tablet splitter and rocked as the blade cut through the tablet, particularly for the second orientation (Table 2). Simvastatin's positioning within the splitter was unstable because of the tablet's shield shape. In contrast to the unusual shapes of lisinopril and simvastatin, the roundness of glipizide facilitated its favorable positioning within the tablet splitter.

The hardness and spherical shape of rofecoxib resulted in difficult, unreliable splitting. (Tablet hardness was assessed by the tester's perception of the force required to split the tablets; rofecoxib tablets were deemed the hardest tablets.) Rofecoxib's extreme hardness required that the tablet-splitter's blade be firmly pressed into the tablet. Subsequently, this great force caused the tablet to uncontrollably rock as the tablet was cut. Rofecoxib also lost the most tablet residue (i.e., "crumbs"), because of the need to press hard on the tablet splitter.

Lovastatin did not exhibit any apparent shape or hardness difficulties, but it marginally failed. Lovastatin is a relatively thick tablet for its small size.

Interestingly, all 4 products from Merck failed, and all non-Merck products passed. These Merck products—lisinopril, lovastatin, rofecoxib, and simvastatin—do not appear to share any one common physical characteristic, except that each has an unusual shape to some extent.

Lovstatin and Lisinopril: Clinical Considerations

For lovastatin, 15% of the half tablets exhibited weights greater than ±15% of target. For one orientation of lisinopril within the tablet splitter (i.e., orientation 1, where the top of this trapezoidal-shaped tablet was placed toward the splitter's blade), 20% of the half tablets exhibited weights greater than ±15% of target. The percent RSD for lovastatin and lisinopril half-tablet weights was just over 10%. A similar degree of failure was previously observed with several other products.[6] Cohen has indicated that this degree in half-tablet weight variability is acceptable since therapeutic outcomes would likely be unchanged.[5]

Given the wide therapeutic index of lovastatin[12,13] and lisinopril,[14] it would appear that splitting these 2 products is acceptable. Gee at al. found that splitting HMG Co-A reductase inhibitors such as lovastatin had no negative effect on lipid panels or liver enzyme tests.[15] Laboratory lipid and liver enzyme tests were conducted before and after 512 patients were enrolled in an HMG Co-A reductase inhibitor tablet-splitting program. Among the patients, 85% of the patients were treated with simvastatin, 15% were taking lovastatin, and 1 patient was administered atorvastatin. Patients were maintained on the same HMG Co-A reductase inhibitor and dose before and after implementation of the program. Laboratory results comparing whole- and half-tablet performance from all 512 patients indicated that there was no change in total cholesterol and triglycerides. Statistically, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) changed favorably, and liver enzymes AST and ALT each increased, although these changes were apparently not clinically significant. These results suggest that a split-tablet program had no effect of HMG (e.g., lovastatin) clinical outcomes.

Rindone found that splitting lisinopril did not change control of stable hypertension.[16] Rindone randomized 28 patients with hypertension, who were on stable doses of lisinopril, into a crossover clinical trial. Patient blood pressures were measured when they were taking whole tablets and split tablets. No statistically significant differences in systolic or diastolic blood pressures were observed between whole-tablet and split-tablet groups.

Simvastatin: Clinical Considerations

Relative to lovastatin and lisinopril, tablet-splitting results for simvastatin were less satisfactory (Table 2). Twenty percent of the half tablets fell outside the ±15% target weight range, with half of those half tablets falling outside the ±25% target weight range. However, 3 studies have assessed the clinical performance of split simvastatin tablets and found favorable results. Using retrospective chart review, Duncan et al. evaluated the effect of splitting simvastatin on patient LDL cholesterol and total cholesterol.[17] Patients were taking simvastatin whole tablets and obtained regular lipid management and cholesterol measurements. Patients were converted to split tablets and maintained the same milligram-per-day dose. There was no statistically significant increase in either LDL or total cholesterol after conversion to split tablets; in fact, each laboratory value decreased. Duncan et al. conclude that half-tablet dosing of simvastatin was as effective as whole-tablet dosing. They also found similar findings for atorvastatin.

In a similar study, Rindone and Arriola converted hyperlipidemic patients from fluvastatin to simvastatin, where patients were instructed to use a tablet splitter to split simvastatin tablets in half.[18] In the 56 patients who completed the study, total cholesterol, triglycerides, and high-density lipoprotein were unchanged, with LDL statistically decreasing. Rindone and Arriola indicate that this substantial cost-savings approach, which, in part, relied on splitting simvastatin tablets, exhibited lipid control in the majority of patients. Most recently, Gee et al. measured laboratory lipids and liver enzyme levels in 512 patients who were enrolled in a HMG Co-A reductase inhibitor tablet-splitting program, where 85% of the patients were treated with simvastatin, as described above.[15] These 3 studies, along with the present split-tablet results and wide therapeutic index of simvastatin,[19] support the mandatory tablet-split policy for simvastatin.

Rofecoxib and Sildenafil: Clinical Considerations

Rofecoxib tablets provided the least desirable half tablets. Fifty percent of the half tablets fell outside the ±15% target weight range, 40% of those half tablets fell outside the ±25% target weight range. Since refocoxib has a high therapeutic index,[20,21] we anticipate that these rofecoxib dose variations will not result in adverse clinical outcomes. The effective daily dose of rofecoxib ranges from 12.5 mg to 50 mg, but the drug is not particularly sensitive to dose. Further, when healthy volunteers were administered up to 5 times the maximum recommended dose for a period of 14 days, no serious toxicities were observed[21]; hence, dose variations from rofecoxib half tablets do not present a toxicity problem.

While sildenafil tablets were not split here and are on the VISN 5 mandatory split list, a clinical study supporting VA policy by Orrico et al. found that the dose of sildenafil citrate could be titrated to the lowest effective dose while incorporating tablet splitting as a method to reduce drug cost.[22] In 96 patients, 58% responded to 50 mg (half tablet) of the drug.

Further Managed Care Considerations

To date, the mandatory tablet-splitting program continues to

offer a substantial costs savings to the VA, both on a local and a national level. Results here support this program, as weight uniformity was generally acceptable for these products. Tablet-splitting initiatives offer the VA, and potentially other managed care organizations, an attractive cost benefit, while maintaining quality health care for health plan members.

As demonstrated here with the several nonmandatory split products tested, other prescription medications may be suitable for a tablet splitting program. For a product to be an appropriate candidate for splitting, several factors should be considered.[1] Sustained-release, enteric-coated, and other dosage forms where tablet splitting would compromise the product's intended release mechanism should not be considered. The product should be relatively flat-priced across dose or have an acquisition cost to the organization that would offer a savings by splitting the higher doses. To maximize savings, tablet splitting should be preferentially considered for more expensive medications. Using these criteria, VA and other health care organizations may prospectively identify prescription medications where mandated tablet splitting will reduce prescription costs while not compromising patient care.

It should be noted that the VA tablet-splitting program is cost-neutral to patients. The patient copayment is $7 for a 30-day supply, although some patients are exempt from providing a copayment because of financial status or service-connected disabilities. Since copayments are based on days of therapy and not drug costs, VA patients do not have a financial motivation to split tablets. However, patients in other health care systems, particularly those patents who pay out-of-pocket for medications, would likely have a greater incentive to utilize tablet splitting. This motivation would be most pertinent to those products that are flat-priced, enabling patients to purchase twice the drug supply for a given cost.

Limitations

The results of this study generally support the mandatory tablet-splitting policy of the VISN 5 region but are subject to limitations. One limitation is that there are no publicly defined acceptance criteria for half-tablet weight uniformity. Hence, alternative criteria can be considered and applied to our results. In our consideration of the data, we applied criteria that we have used previously.[6] These criteria are more liberal than the USP test for whole tablets, in part since the USP test allows only an initial RSD of no more than 6%, while the criteria that we applied allowed 10% RSD. If an initial 6% RSD limit were applied, several of the products in Table 1 that we found to pass would require further evaluation (i.e., "Stage 2" testing) and could possibly fail. Additionally, half tablets were assessed for dose uniformity immediately after being split; half tablets were not placed back into a prescription vial, where they may be subjected to attrition. At this time, we know of no specific evidence to favor any particular acceptance criteria for weight uniformity of half tablets. It has been suggested that patients, caregivers, and health systems would benefit from public quality standards for half tablets.[6,7]

A second potential limitation of this study is the use of a trained pharmacy student to perform the tablet splitting. It is possible, and even likely, that different outcomes would result, depending on who performed the splitting. It would be perhaps desirable to evaluate the ability of various individuals and patients to split tablets and to elucidate the individual patient factors that contribute to successful tablet splitting. Given the positive results of our study, further research would be desirable to determine if VA patients can obtain similar favorable weight uniformity to better replicate the real-world environment. Other studies have assessed the ability of patients to split tablets. McDevitt et al. evaluated the ability of healthy volunteers to split hydrochlorothiazide tablets by hand.[23] Gender, age, education, or tablet-splitting experience were not found to be predictive of the ability of individuals to split tablets. Peek et al. evaluated the ability of patients to split simvastatin, metoprolol, warfarin, and lisinopril tablets.[24] Individual patients were assigned to one of 4 groups that differed in brand of tablet splitter and whether patients were instructed in the method of tablet splitting. Peek et al. found that both the brand of the tablet-splitting device and instruction improved tablet-splitting accuracy. Patient experience also resulted in more accurate splitting of warfarin tablets.

A third potential limitation was our use of a specific device to split tablets. Peek et al. found that one splitter performed better than another splitter.[24] The suggestion that different tablet-splitting devices can yield markedly different uniformity results reflects our previous anecdotal experience with a tablet-splitting device different from the device used in the present study. In our previous experience, the commercially available tablet splitter appeared to be of lower quality and poor design; a razor blade was simply glued onto a plastic housing at an angle not perpendicular with the plastic housing, resulting, commonly, in properly centered tablets splitting into approximately one third/two third "halves." The poor design and performance of this earlier device caused us to abandon the use of a tablet splitter and rely on splitting tablets with a simple razor blade, by hand.[6] Hence, we suspect that the quality of the tablet splitter can directly affect half-tablet weight uniformity, and our results using the ACE-LIFE Pill Splitter model PS12E may not be applicable to all tablet-splitting devices.

We also did not measure patient outcomes. Tablet splitting could have an adverse effect on patient compliance. Several studies have examined the influence of patient tablet splitting on compliance and generally indicate that most patients accept tablet splitting. For example, Carr-Lopez et al. studied 233 patients, aged 35 to 87 years, who were prescribed 40 mg tablets of lovastatin and instructed to split them into two 20 mg doses.[25] Most patients reported that the tablet splitter was easy

use and did not affect their compliance. However, 6% reported that the tablet splitter was difficult to use, and they would not split tablets even to save money. Mendez et al. found similar results for patients taking half tablets of simvastatin, although 40% of patients believed that splitting would influence compliance.[16] Fawell et al. studied the relationship of tablet splitting and compliance, drug acquisition cost, and patient acceptance for fosinopril sodium.[27] Patients accepted tablet splitting, and the splitting of fosinopril sodium tablets reduced the drug acquisition costs in the health system without affecting patient compliance.

Another potential limitation is the unknown clinical significance of dose variability in half tablets. The focus of our work was on products relevant to the VISN 5 region. Other products of interest may include drugs with a narrower therapeutic index. Dose variability is expected to be of greater potential importance for drugs with a narrow therapeutic index. Warfarin was evaluated here and is considered a narrow therapeutic index drug. Given the small dose variations observed here for warfarin half tablets and the lack of evidence to suggest any adverse clinical effects of such small dose variations, we anticipate tablet splitting of warfarin to have no clinical consequence.

Conclusion

revious observations from experience with razor blade tablet splitting showed that a majority of tablets did not split evenly and that visible tablet features did not predict success or failure of the half tablets to pass the weight-uniformity test. However, our results for weight uniformity in the current study were favorable and generally support the mandatory tablet-splitting policy of the VISN 5 region. We interpret our results to indicate that a tablet-splitting policy is a viable approach to provide patients with dosage forms with acceptable weight uniformity. There is, however, a need for quality standards for half tablets to permit health care providers to better delineate the acceptability of tablet-splitting policies.

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DISCLOSURES

No outside funding supported this study. Author James E. Polli served as principal author of the study. Study concept and design were contributed primarily by Polli and author Brian R. Martin. Analysis and interpretation of data were contributed by Polli and author Sharon Kim. Drafting of the manuscript was the work of Polli and Martin, and its critical revision was the work of Polli and Kim. Statistical expertise was contributed by Polli. Polli has been principal investigator for grants from Forest Laboratories.

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Evaluation of the Reproducibility of Tablet Splitting to Provide Accurate Doses for the Pediatric Population

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Abstract

Portions of tablets are commonly administered to pediatric patients with virtually no data to demonstrate that the correct dose is consistently delivered to the patient. This study was conducted to assess the reproducibility of tablet splitting with two different commercially available tablet splitting devices. Twenty tablets were randomly selected and split into halves and, if clinically appropriate, into quarters. Each part was weighed and assessed for statistically significant differences. Tremendous variability was found to exist between doses. Some tablet parts could not be reproducibly cut into parts with either cutter. Therefore, it was concluded that solid dosage forms should not be cut, especially into quarters. Patients cannot be assured of receiving the prescribed dosage on a consistent basis.

Introduction

Children are especially exposed to the dangers of medication errors. The risk of drug administration errors is high in the pediatric population due to differing age, size, and development and function of organs, such as the liver and the kidney. Pediatric dosages must be calculated on a weight basis, such as milligram per kilogram, or by body surface area. Certain drugs may not be readily available in suitable formulations, strengths, and concentrations for pediatric patients. Consequently, the risk of medication errors in these patients is increased since often the alteration of available dosage forms is required.[1-3]

The difficulty in assuring the delivery of an accurate dose of liquid medication has been appreciated.[4] There are occasions when a fraction of a solid dosage form may be required. Issues related to tablet splitting include: homogenous distribution of active ingredient, the point at which an unscored tablet should be split, and the most appropriate device for splitting tablets. Although portions of tablets are commonly administered to pediatric patients, it is done with virtually no data to support these actions.[5-6]

Only two studies have attempted to address these questions. Stimpel, et al.[5] evaluated fourteen brands of antihypertensive agents to determine how evenly the tablets would break along the scoring line. Most tablets broke easily, but deviations in half-tablet weights of up to 10% were frequent. Another study conducted by Sedrati, et. al.[6], examined the accuracy of a tablet splitting device with various shapes and sizes of tablets. They found the device was most accurate with larger tablets (> 600 mg), oblong tablets, and those that had flat edges.

We conducted a study with captopril, clonidine, amlodipine, atenolol, carbamazepine, and sertraline tablets to assess the reproducibility of tablet splitting using two different commercially available pill cutters. Tablet halves were evalu-

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ated for all medications and quarters were evaluated with clonidine and captopril. The purpose of this study was to determine whether a statistically significant difference between tablet parts could be demonstrated.

Methods

Drugs to be evaluated were chosen by surveying physicians at our institution to determine what tablets they were commonly seeing split into parts. The chosen medications are listed in the Table. Three lots were obtained for each medication. Capoten® (captopril) and clonidine were provided by their pharmaceutical manufacturers. All other medications were obtained from the University of Kentucky outpatient pharmacy. After an initial practice session, two sets of twenty tablets were randomly selected from each lot, individually weighed on a Mettler AT201 analytical balance (sensitivity to 10 µg) (Mettler Instrument Corporation, Highstown, NJ), and split with two different commercially available pill cutters into halves and into quarters if appropriate based on usage. Each part was weighed on the analytical balance. For simplicity, these cutters will be referred to as the "beige" cutter (EZ Dose, Bumsville, MN) (Figure 1) and the "blue" cutter (Health Care Logistics, Inc., Circleville, OH) (Figure 2). A new pill cutter was used for every one-hundred cuts to minimize any variation due to dulling of the blade. If a tablet was scored, an attempt was made to place the tablet in the cutter so that the blade would cut along the scoring line. If the tablet was not scored, the tablet was placed on the designated area in the cutter, and cut as close to the center as possible. Obvious physical and visual differences between tablet parts were noted by an independent observer. Homogenous distribution of the active ingredient throughout the entire tablet was assumed.

Descriptive statistics were used to assess the mean and the standard deviation of total tablet weight, the weight of the half, and the weight of the quarter. Normality of data distribution was assessed via observation of the similarity or closeness between standard deviations and was determined to be normally distributed. A two-tailed t-test, therefore, was used to test for differences between tablet halves. To test for differences between tablet quarters, a one-way ANOVA was used. A p value of < 0.05 was considered significant.

To address the uniformity of dosage units,[7] the USP may consider an analytical assay of the active ingredient to be the most appropriate method to assess differences between tablet parts. A practical measure, however, examining weight variation between tablet parts was employed in this trial.[7] If the variation in tablet weight is statistically significant, it could be deduced that the fraction of active ingredient delivered would be different for each part. Also, according to USP, to meet the uniformity of dosage unit requirements,

Figure 1. "Biege" cutter (EZ Dose, Bumsville, MN)

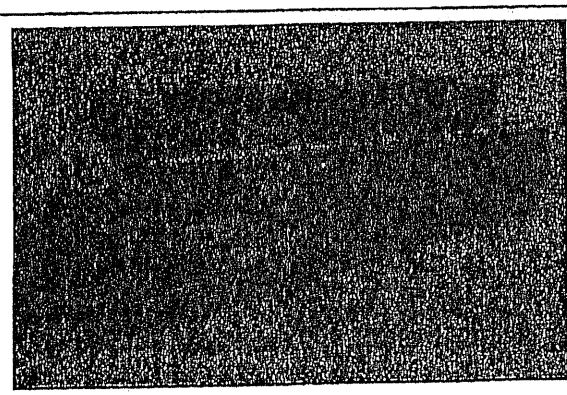

Figure 2. "blue" cutter (Health Care Logistics, Inc., Circleville, OH)

Table

Drug	Lot	Blue Cutter				Biege Cutter			
		% halves weighing within ± 15%	p-value	%quarters weighing within ± 15%	p-value	% halves weighing within ± 15%	p-value	% quarters weighing within ± 15%	p-value
[1]Catapres 0.1mg[S] (136mg ± 1.91)	63003B	81.3	< 0.001	47.5	< 0.001	90.0	0.725	68.8	0.628
	63002C	52.5	< 0.001	43.8	< 0.001	85.0	0.010	71.3	0.158
	064001B	100.0	< 0.001	60.0	< 0.001	90.0	0.001	57.5	0.076
[2]Clonidine 0.1mg[S] (70.06mg ± 2.16)	2572-038	55.0	< 0.001	45.0	0.001	78.9	0.013	31.6	0.163
	058H32	47.5	< 0.001	41.2	< 0.001	62.5	0.159	48.8	0.341
	130C41	70.0	< 0.001	37.5	< 0.001	30	0.006	25.0	0.013
[3]Capoten 12.5mg[S] (51.65mg ± 0.55)	MAE015	67.5	< 0.001	37.5	< 0.001	95.0	0.053	28.8	0.084
	MCE026	58.3	< 0.001	48.6	< 0.001	100.0	0.027	36.1	0.005
	L3J26A	95.0	< 0.001	55.0	0.007	100.0	< 0.001	26.3	0.003
[4]Amlodipine 5mg[NS] (199.5mg ± 2.39)	D223D	85.0	0.002			90.5	0.417		
	H121A	85.7	0.120			76.9	0.009		
	A863H	77.5	0.040			77.5	0.070		
[5]Tenormin 25mg[NS] (58.5mg ± 1.00)	HA181	95.0	0.345			35.0	< 0.001		
	HA051	62.5	< 0.001			27.5	0.009		
	HA201	87.5	0.012			25.0	0.012		
[6]Sertraline 50mg[S] (155.5mg ± 2.5)	A593F	100.0	0.408			100.0	0.463		
	F533A	100.0	0.076			100.0	0.101		
	3JP050A	100.0	0.495			90.0	0.001		
[7]Tegretol 100mg[S] (405.2mg ± 4.66)	1T168197	92.5	0.1098			65.0	< 0.001		
	1T160545	92.5	0.006			80.0	< 0.001		
	1T165813	87.5	0.215			60.0	0.099		

S = Scored into halves; NS = Not scored

1. Boehringer-Ingelheim Pharmceuticals, Inc., Ridgefield, CT
2. Rugby, Norcross, GA
3. Bristol-Meyers Squibb Co, Princeton, NJ
4. Pfizer LABs, New York, NY
5. Zeneca Pharmaceuticals, Wilmington, DE
6. Pfizer, Roerig Division, New York, NY
7. Ciba Geneva, Summit, NJ

dosage units must contain within ± 15% of their label claim and the relative standard deviation must be < 6%.[7] Therefore, a significant difference was also represented by tablet parts which fell outside the ± 15% of the desired mean percentage of label claim.

Results

Statistically significant differences were demonstrated when cutting clonidine tablets into halves (p-values < 0.001). (Table) The brand name, Catapres®, reproducibly cut better than the generic clonidine. In fact, one lot of the brand name clonidine (Catapres®) demonstrated the ability to be reliably split into parts, as 100% of tablet parts fell within the desired specifications of ± 15% of the desired weight. The range was 52.5% to 100%. In contrast, 78.9% of the generic clonidine tablet halves fell within the desired specifications at best case and only 30% at worst case. As a general rule, fewer than 50% of quarters were within USP accepted standards. Similar results were obtained with captopril tablets.

In general, the beige cutter appeared to be more accurate when cutting halves. However, neither cutter demonstrated satisfactory results when cutting quarters. Statistical analysis to determine the superiority of one tablet splitter over the other was not conducted, because neither splitter reproducibly cut tablets into the desired parts.

Because of the tremendous variability observed in phase one between tablet quarters, tablets in the second phase of this study were only split into halves. (Table) As in the first phase of this study, all of the drugs, except sertraline, could not be reproducibly cut into halves. In fact, only 25% to 35% of Tenormin® (atenolol) tablet halves weighed within ± 15% of the desired mean percentage of the total tablet weight. Unlike the first phase, the beige cutter yielded less reproducible results than did the blue cutter. However, neither cutter yielded consistent results.

Obvious physical differences could be observed in greater than 50% of tablet halves. Some tablets, such as Tegretol® (carbamazepine) 100mg chewable tablets, even crumbled into multiple pieces when split into parts. The pieces were weighed together as accurately as possible, unless the tablet was pulverized.

Discussion

Enormous variability exists between doses when tablets are halved or quartered. This data likely represents the best case scenario with respect to the accuracy of tablet splitting. In the real world, tablets are split by parents into parts with knives, razor blades, fingers, and other such devices. Occasionally, parents may have a tablet splitting device available to them. However, even with these devices, the inability for tablets to be reproducibly split into a desired part has been demonstrated. Moreover, if the assumption that the active ingredient is homogeneously distributed throughout a tablet is not valid, the potential for even larger variation in dosage exists. Although no pharmaceutical company will guarantee homogenous distribution of active ingredient, even for scored dosage forms, it is assumed daily by physicians and pharmacists. Analytical studies would be required to evaluate this further.

Pediatric practitioners and pharmacy administrators need to evaluate their policies and beliefs regarding the manner in which small dosages are delivered to pediatric patients. Alternative dosage forms should be investigated. Extemporaneous compounding of solutions, suspensions, suppositories, or powder papers may be required. For example, due to the significant variability demonstrated with captopril, these tablets are no longer cut into parts at our institution. In light of a recent study of captopril in solution,[8] we are now dispensing only liquid dosages of captopril to our pediatric patients.

Clonidine was chosen in this study to examine the clinical dilemma of delivering small doses (e.g. 25µg by mouth) to our pediatric patients with attention deficit hyperactivity disorder. This therapy is being used more frequently for many pediatric patients.[9] Dosing variability (e.g. differences in tablet weight) could affect the ability to assess successful drug therapy for this condition. Differences in tablet size and manufac-

turers for a given product may exacerbate these differences and complicate patient assessment. The approximate twofold greater initial tablet weight and size of Catapres® may explain the increased variability observed with generic clonidine.

A follow-up prospective evaluation of whether a correlation exists between variations in dose and clinical outcomes would be informative. This information would allow the full implication of the dosage variations to be appreciated. Until this information is known, however, tablets should not be split into parts for pediatric patients. Tablets should not be cut, especially into quarters. Patients cannot be assured of receiving the prescribed dosage on a consistent basis. The ultimate effect of this variation on patient outcome, however, remains to be determined. If tablets are split the health care team needs to carefully evaluate the patient and take into consideration this dosage variability in the desired outcome of their patient.

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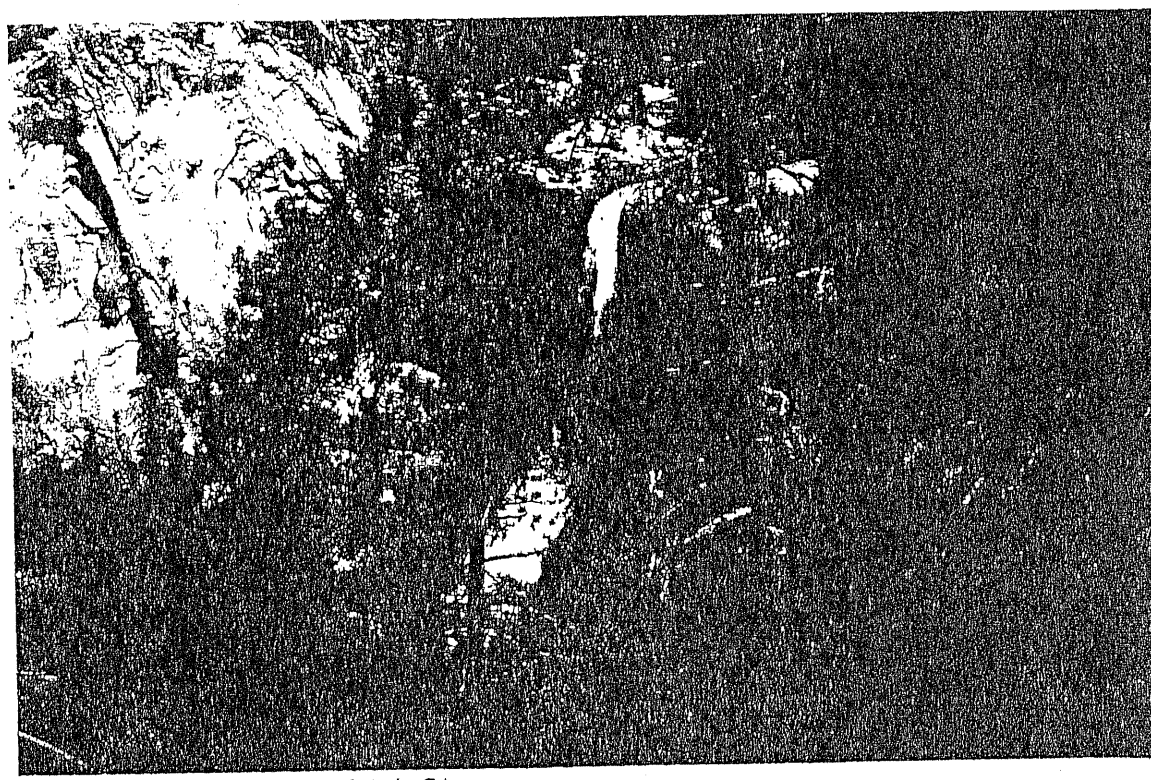

Nevada Falls, Yosemite National Park, CA

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The Practice of Splitting Tablets

Cost and Therapeutic Aspects

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Abstract

Background: Tablet splitting is used in pharmacy practice to adjust the dose to be administered. It is also being advocated as a method of reducing prescription drug costs.

Methods: The potential for using this practice as a cost-saving method was examined. The top 200 prescription products in Canada were evaluated for their potential for tablet splitting to reduce costs.

The assessment was based on the dosage form (only tablets could be split), availability of dosages in multiples, whether the drug was used for long-term therapy, whether the product was packaged suitably (e.g. oral contraceptives in a therapeutic package), whether pricing structure would allow substantial saving, and the physical nature of the tablets (e.g. whether there were special dose-release characteristics). The products most commonly split in three Canadian pharmacies were compared with the products that had a substantial savings potential. Costs for splitting tablets in the pharmacy and costs of instructing patients to split tablets were calculated.

Results: Savings could be generated from tablet splitting for only 15 of the 200 products. There was little overlap between these 15 products and the products that were most frequently split in the three pharmacies. The costs associated with tablet splitting in the pharmacy were approximately 0.1 Canadian dollars ($Can) per tablet. The cost of instructing a patient to split the tablets was approximately $Can1.

Conclusions: Tablet splitting appears to have limited usefulness as a cost-reduction strategy. Only a small proportion of products are suitable for splitting and have the potential for savings. There are also costs arising from splitting tablets in the pharmacy, or instructing patients to do so, and from wastage of product. There are also issues such as patient compliance and the risk of an incorrect dose being taken that should be considered.

Tablet ('pill') splitting is an accepted practice in dispensing medication. It has been used when a dosage form of the required strength is not available commercially. This is a common clinical problem in prescribing low-dose therapy for elderly patients.[1] More recently, the practice has been used in some countries as a method to control prescription expense. With the increasing cost of medication this practice may become more common.

Splitting tablets for the purpose of providing a lower dose is done under various circumstances, including providing medication for a child or older person when the dosage form is not available in the prescribed strength, when tapering a dose, or when titrating the dose. Tablet splitting is one of many

techniques used by pharmacists and nurses to provide medication in the proper dosage.

A number of medications are used at doses much smaller than those traditionally used. For example, hydrochlorothiazide is commonly used at a dose of 12.5mg, but the lowest dose tablet currently available is 25mg. Thus, patients need to split tablets in order to receive the smaller dose. This approach contributes to a more cost-effective approach to treating hypertension.[2]

Slow titration refers to starting a medication at a low dose and slowly increasing the dose to the target level. One example of the benefits of tablet splitting for slow titration is in patients post-myocardial infarction (MI). Often patients post-MI cannot tolerate full doses of β-blockers used in clinical trials and are often given a very small initial dose of a β-blocker, such as metoprolol 12.5mg, in order to see how they tolerate the drug. If the patient tolerates this dose, the dosage is gradually increased to reach the dosage used in comparative clinical trials. However, the smallest dose metoprolol tablet is 50mg, which requires that the tablet be split into quarters to provide the 12.5mg dose. The procedure of splitting tablets thereby allows for ease of dosage management by the patient, because only one tablet dosage is required. If several different dosages of tablet were used, this would have the potential of increasing the errors in taking medication, as well as increasing the cost of the medication to the patient.

Patients who are receiving anticoagulation therapy with warfarin may require frequent dosage changes to maintain an appropriate level of anticoagulation, especially when starting therapy. Patients are often prescribed warfarin 2mg tablets when therapy is initiated. This allows for modification of dosage by using one or more tablets, or breaking the tablets in half for smaller increments. Instead of purchasing numerous different dosage tablets, the patient would purchase one dosage of tablet, and then adjust the dosage as directed.

The accuracy that can be achieved in splitting tablets varies with the size of the tablet and its characteristics.[3,4] For example, when halving small tablets there was a variation in weight of more than 20 for 44% of the tablet halves. This is outside the compendial limits of variation for tablets. It appears that for reasonable accuracy in dosage, tablet splitting should be restricted to large or scored tablets. This has been confirmed in an evaluation of a commercial product for splitting tablets. The Pill Splitter (LGS Health Products, Beachwood OH) was found to be effective in splitting all the tablets tested, with best results from large tablets (tablets approaching 0.5cm in size take longer to position for cutting) and those that were coated (film rather than sugar coated, for example).[5]

In one small study comparing tablets that were split (40mg atorvastatin) with an equal dose of the formulated product (20mg), there were no differences in clinical outcomes, as measured by low-density lipoprotein cholesterol levels, in patients followed for 12 weeks.[6] This study also demonstrated that there were no significant clinical implications relating to compliance/adherence with therapy when tablets are split.

The patient may be required to perform the tablet splitting and this would be indicated in the label directions, or verbally by the pharmacist. Alternatively, the tablets may be split by the pharmacy staff at the time of dispensing. There do not appear to be any problems of compliance or patient acceptance of therapy when split tablets are used.[7]

Some countries have specifically set out instructions for splitting tablets; for example, Barbados, through the Barbados National Drug Formulary.[8] Some health management organisations (HMOs) in the US also have guidelines for the splitting of tablets to effect savings. An instruction sheet from one HMO entitled 'Half-tablets: cost-effective and easy to do!' states that the purpose is to save money.[9]

The cost savings achieved through tablet splitting may accrue either to the patient, where they must pay for their own medications out of pocket, or to a drug benefit programme. For many drugs, generic products are available at reduced cost. For newly marketed medications that do not yet have generic equivalents (e.g. an HMG-CoA reductase inhibitor, or 'statin'), the splitting of tablets may

provide substantial cost savings for the patient. They may be able to obtain a full prescribed dose of the medication at a fraction of the cost, by obtaining tablets containing twice the required dose and splitting them.

Tablet splitting has several drawbacks.

- *Unsuitability of some dosage forms:* Controlled release tablets have been designed to release the medication in a predictable manner over time. To do this a variety of methods have been used. Some methods, such as the use of coated granules, may be suitable for tablet splitting. Other dosage forms, however, would have their designed features impaired by splitting. The difficulty in assessing the suitability of each controlled dosage form and the probability of impairing their function makes it impractical to include these tablets for tablet splitting.
- *Wastage:* Because of poor technique or tablet characteristics, the tablets may crumble or shatter when splitting is attempted. This leads to wastage of the product, as the tablet fragments cannot be used because of dose inaccuracy. The loss from tablet wastage may significantly decrease the benefits of tablet splitting.
- *Incorrect dose:* For the reasons mentioned above, the patient may split tablets unevenly, resulting in an incorrect dose being administered. This would be a significant concern if it occurred with a drug with a narrow therapeutic index, such as digoxin. While 0.25mg tablets are available, it would be dangerous to have the patient split tablets to provide 0.125mg. It may also be difficult to split irregularly shaped tablets evenly.
- *Confusion/noncompliance:* Even patients who have excellent records of compliance may become confused about their regimen, especially if their medication dose is frequently adjusted or requires splitting tablets. In one reported case, a patient receiving two and a half 1mg warfarin tablets was prescribed 0.5mg warfarin tablets and continued to take two and a half tablets, not realising the difference in dose.[10] A patient may not read the label accurately and take a full tablet instead of splitting the tablet. If the pharmacy supplies the tablets already split, the patient may not realise that the tablets are already split and choose to split the half tablets again, thereby receiving only 50% of the prescribed dose. Patients who require a regimen including split tablets need to be counselled about how to administer and split the tablets. Compliance may be increased by having the pharmacy staff split the tablets and dispense them in an appropriate form of compliance packaging. This would increase the cost of providing the medication.

Older patients or patients with disabilities may have difficulty splitting tablets, either manually or with a tablet splitter.[11,12] Those with vision or manual dexterity problems may find tablet splitting very difficult. In a study of acute geriatric patients, 94 (78.3%) were unable to open a container or break a scored tablet.[11] Even using tablet-splitting devices may be challenging for these patients, because good eyesight and manual dexterity are essential to place the tablet in the cutting device, line it up appropriately, and ensure the tablet is evenly split before administering the product. Patients may also have difficulty splitting tablets if the tablets are not scored.

If they do not receive assistance, patients may become frustrated to the point that they become nonadherent to the prescribed regimen. They may try to adapt their regimen to their abilities, by taking a full tablet every other day. However, this type of alternate-day regimen can be dangerous. Patients must be continually encouraged, counselled and monitored if they are to succeed on a regimen that involves splitting tablets. This requirement for more professional time is a cost that will offset some of the economic gains from tablet splitting.

With the use of tablet splitting as a means of reducing prescription costs, there is a need to analyse the potential benefits and drawbacks to this practice. This paper sets out some of the potential savings available from the practice of tablet splitting, based on the top 200 products on the Cana-

dian market, and factors that constrain the possible savings.

Methods

Cost-Saving Potential

The top 200 prescription drugs in Canada, based on number of prescriptions, were selected to determine the potential for tablet splitting as a mechanism to reduce prescription price.[13] The proportion of tablets suitable for splitting and the cost of the tablets for each dosage were determined for each drug.

The suitability for splitting was determined based on the dosage form (only tablets could be split), availability of dosages in multiples, whether the drug was used for long-term therapy, whether the product was packaged suitably (e.g. oral contraceptives in a therapeutic package), whether the pricing structure would allow substantial saving (more than $Can0.10 per tablet – roughly the salary expense for a pharmacy staff member to split the tablets; 2000 values), whether they had special dose-release characteristics and the nature of the tablets (e.g. spherical or irregular tablets are difficult to split). The cost of a tablet-splitting device ranges from $Can6 to $Can10.

Comparison with Current Practice

Information was sought on the pharmaceutical products that are routinely split in practice. To identify these products, three Canadian (Edmonton) pharmacy managers specialising in geriatric services were asked to prepare a list of products they commonly split. These were then compared with the top 200 products list.

Time Required to Split Tablets in Pharmacy

The time required to split tablets in the pharmacy was determined by using a stopwatch. Two pharmacy students used a tablet splitter to split 20 tablets of four different products selected as a convenience sample. The average time was calculated from these data and was used to calculate the cost to cover the added time cost in tablet splitting. This would be done in cases where the patient was unable to split the tablets accurately.

Time to Counsel Patients on Tablet Splitting

A pharmacy student counselled eight actual patients on tablet splitting. The procedure was timed by the pharmacy student using a stop watch.

Results

Cost-Saving Potential

The top 200 products had a variety of dosage forms, of which 148 were tablets. These tablets consisted of various tablet forms (sugar- or film-coated, sustained-release, sublingual). A number of products were found to be unsuitable for splitting because of their therapeutic characteristics or presentation. This reduced the potential number of products to 127. About 70 of the products were generic or low-cost products that would yield little saving from tablet splitting. For the remaining products, many had dosages that were not in multiples that could be used for tablet splitting, for example a 10mg and a 25mg tablet.

By narrowing the list to medications that are for long-term therapy, tablets that can be easily split and those for which there is a gain of at least 10 cents, the number of drugs was reduced to 15 [enalapril (Vasotec®[1]), warfarin (Coumadin®), simvastatin (Zocor®), pravastatin (Pravachol®), atorvastatin (Lipitor®), lisinopril (Zestril®), fosinopril (Monopril®), lisinopril (Prinivil®), quinapril (Accupril®), risperidone (Risperdal®), sumatriptan (Imitrex®), alendronate (Fosamax®), nefazadone (Serzone®), cilazapril (Inhibace®) and lovastatin (Mevacor®)]. They represent only 14 chemical entities and include four statins and five ACE inhibitors (table I).

The potential savings from tablet splitting for these products are substantial. Many of the products have similar prices for each of the dosages, so

1 Use of tradenames is for product identification only and does not imply endorsement.

Table I. Potential cost savings from tablet splitting of 15 products

Drug	Dose (mg)	Price per tablet (Canadian dollars; 2000 values)	Dose (mg)	Price per tablet	Saving (%)
Quinapril (Accupril®)	5	0.82	10	0.82	50
	20	0.82	40	0.82	50
Cilazapril (Inhibace®)	2.5	0.68	5	0.79	41
Fosinopril (Monopril®)	10	0.79	20	0.95	40
Enalapril (Vasotec®)	2.5	0.68	5	0.68	50
	5	0.68	10	0.96	29
	10	0.96	20	1.16	40
Lisinopril (Zestril®)	5	0.67	10	0.87	34
Lisinopril (Prinivil®)	10	0.87	20	1.05	40
Atorvastatin (Lipitor®)	10	1.16	20	2	38
	20	2	40	2.15	46
Lovastatin (Mevacor®)	20	1.73	40	3.19	8
Pravastatin (Pravachol®)	10	1.15	20	1.79	22
	20	1.79	40	2.15	40
Simvastatin (Zocor®)	5	0.9	10	1.78	1
	10	1.78	20	2.2	38
	20	2.2	40	2.2	50
	40	2.2	80	2.2	50
Risperidone (Risperdal®)	0.25	0.42	0.5	0.7	17
	0.5	0.7	1	0.96	31
	1	0.96	2	1.92	0
	2	1.92	4	3.83	0
Nefazadone (Serzone®)	50	0.73	100	0.8	45
	100	0.8	200	0.93	42
Alendronate (Fosamax®)	5	1.38	10	1.76	42
Sumatriptan (Imitrex®)	50	12.95	100	14.27	45
Warfarin (Coumadin®)	1	0.32	2	0.34	47
	2	0.34	4	0.42	38
	2.5	0.33	5	0.36	45
	5	0.36	10	0.57	19

savings of up to 50% are possible. Most savings are in the range of 30 to 50%. Maximum savings are obtained for quinapril, for which all dosages are priced the same.

Comparison with Current Practice

The list of tablets that were reported to be commonly split in three Edmonton pharmacies is as follows: amlodipine, atenolol, benztropine, calcium (unspecified), carbamazepine, clonazepam, Dyazide®, hydrochlorothiazide, indapamide, loxapine, methylphenidate, metoprolol, oxybutynin, paroxetine, risperidone, sildenafil, sotalol, Stresstabs® (a high potency multivitamin product classified as a dietary supplement), warfarin and zopiclone (table II). The lists from each pharmacy had little overlap. They represent routine medication for chronic disease.

For the listed products that were reported as being split in Edmonton, there is an overlap of only two products from the top 200 products: risperidone and warfarin. Savings were not substantial, with only 4 of 19 showing savings of more than $Can10 for an average prescription representing a 1-month supply of medication. Six of the products did not have double-strength products that would generate savings by splitting.

Time Required to Split Tablets in Pharmacy

The results are presented in table III. The products used for timing were Desyrel® 50mg (trazodone), Norvasc® 10mg (amlodipine besylate),

Novo-cimetine® 600mg (cimetidine) and Apo-Trimip® 25mg (trimipramine maleate).

The cost associated with tablet splitting was based on an hourly rate of $Can60, which is representative of charges for pharmaceutical services in Canada.[14] Based on an average time for tablet splitting of 5 seconds per tablet (table III), the service cost of splitting was $0.0833 per tablet. This indicates that a cost of almost 10 cents per tablet would be incurred to cover the pharmacy cost of splitting tablets. The use of technicians or trained staff to split tablets may reduce the cost. If the patients split the tablets themselves, this pharmacy cost is avoided.

Other costs would be incurred in implementing a tablet-splitting procedure. The first of these is the product expense resulting from wastage when the tablets shatter or break unevenly. This cost is one that both pharmacy and patient might incur. Additional salary cost to cover the added calculation and record keeping is required.

Time to Counsel Patients on Tablet Splitting

Counselling time for eight patients on tablet splitting ranged from 37 to 80 seconds (table IV). The patients ranged in age from 54 to 68 years. For the four patients who had split tablets previously, the average time was 57.5 seconds. The four patients who had not split tablets previously required an average of 64 seconds. Overall, the average time for counselling was 60.75 seconds. At an hourly cost of $Can60, the counselling expense would be about $Can1.00.

Discussion

From this limited sample it appears that in current practice, tablet splitting is more likely to be for clinical, than for economic, reasons. However, there appears to be some benefit in using tablet splitting as a means of reducing drug costs, and the procedure is used widely, both in Canada and elsewhere. The procedure can generate savings, not only for new, expensive products, but also for many products that have moderate costs. In Barbados, a small study of six drugs used in cardiovascular disease showed prescription savings from tablet splitting in the range of 15 to 35% (personal communication, Pamela Payne, 2001 Aug).

Similarly, HMOs in the US seek out savings and insist on tablet splitting for many products. The

Table II. Potential cost savings from tablet splitting in 3 pharmacies

Drug	Dose (mg)	Price per table ($Can; 2000 values)	Dose (mg)	Price ($Can; 2000 values)	Average no. of tablets/prescription	Saving ($Can)
Amlodipine	5	1.23	10	1.82	44	14.08
Atenolol	100	0.11			51	
Benztropine	2	0.02			35	
Carbamazepine controlled release	200	0.21	400	0.42	92	0
Clonazepam	0.05	0.12	1	0.19	49	1.23
Dyazide[a]	0.05				40	
Hydrochlorothiazide	25	0.04	50	0.04	51	1.02
Indapamide	1.25	0.19	2.5	0.3	50	2
Loxapine	50				45	
Metoprolol	50	0.12	100	0.22	111	1.11
Oxybutynin	5				62	
Paroxetine	10	1.49	20	1.59	38	26.41
Risperidone	0.5	0.7	1	0.96	38	8.36
Sildenafil	50	10.8	100	10.8	6	32.4
Sotalol	80	0.59	160	0.65	78	20.67
Warfarin	2	0.34	4	0.42	62	8.06
Zopiclone	75	0.47			34	

a A combination product containing triamterene 50mg and hydrochlorothiazide 25mg; $Can = Canadian dollars.

Table III. Average time (sec) to split four different products

Product	Student 1	Student 2
Trazodone (Desyrel®) 50mg	4.05	4.35
Amlodipine (Norvasc®) 10mg	5.4	5.0
Cimetidine (Novo-cimetine®) 600mg	5.5	6.0
Trimipramine (Apo-Trimip®) 25mg	4.1	4.4
Mean time (sec)	4.76	4.94

avoidance of expense by tablet splitting is recommended in the US by various nonprofit groups such the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, as well as the publication Consumer Reports. An incentive for patients to economise is the requirement that they pay the full cost, or a substantial portion of the costs, of medication that is not covered by a drug benefit programme.

In countries where medication is dispensed in the original treatment pack (thus creating an obstacle to pharmacists splitting tablets for patients), it is possible for patients to realise savings as long as the pricing structure results in similar prices for varying doses. The disincentive for this to occur in many European countries is the extensive health insurance coverage for medication, which requires patients to pay only a portion of the cost. For this reason the use of tablet splitting as a method of generating health cost savings may be appropriate only for some countries.

The potential for using this method to reduce costs is severely restricted by the small number of products suitable for tablet splitting. The practice is largely dependent on the actions and policies of pharmaceutical manufacturers. Changes in pricing policies could create a substantial reduction in possible savings. Pharmaceutical firms also have the capacity to encourage or hinder the practice of tablet splitting by the dosage forms they produce. The number of dosages available, the characteristics of the tablet, the use of controlled-release dosage forms and packaging all have an effect.

Errors involving split tablets are likely to result in double or half the dose being taken, which can be harmful to the patient. Widespread use of tablet splitting may increase the inappropriate use of medication, a problem that is now serious and in need of redress. To minimise problems, there is a need for effective instruction by pharmacy or other healthcare personnel, as well as some form of continual monitoring of drug use to detect inappropriate dosages being taken.

Patients have a major role in understanding the relationship of dosage to dosage forms, so that they are not confused by the splitting of tablets. They should be able to split the tablets easily, either by hand or with a tablet splitter. To achieve the therapeutic and economic benefits from tablet splitting, patients need to be educated on the rationale and procedures of tablet splitting. This process takes time and incurs a cost. For instruction on tablet splitting, counselling takes only about 1 minute. If more detailed counselling were required, based on dosage or disease factors, the time would be longer.

In cases where medication is prepared by the pharmacist, there is less problem with an inappropriate dose being used in an institutional setting, or if the medicine is dispensed in compliance pack-

Table IV. Time required to counsel patients on tablet splitting

Patient age (y)/gender	Drug	Repeat treatment?	Time (sec)
57 M	Hydrochlorothiazide 25mg	Yes	37
61 M	Hydrochlorothiazide 25mg	No	80
67 M	Atenolol 50mg	Yes	69
54 M	Atenolol 50mg	Yes	49
61 M	Atenolol 50mg	No	60
62 M	Paroxetine 20mg	Yes	75
68 F	Paroxetine 20mg	No	57
65 F	Metoprolol 50mg	No	59

F = female; M = male.

aging (weekly medication boxes or bubble packs) for ambulatory use. For ambulatory patients, medication provided without compliance packaging would require some patient instruction. There is, however, a cost generated by the preparation of the medication. At a cost of 10 Canadian cents per tablet for tablet splitting, a prescription of 100 tablets would cost an additional $Can10.00. Compliance packaging would also incur additional costs.

Private or public drug benefit programmes have the greatest potential gain from a general trend towards tablet splitting to save on pharmaceutical expenditures. They can select products where savings will be realised and set out guidelines for the tablet-splitting procedure. There may be substantial cost savings for some expensive products. This is best realised for long-term therapies where the patients can consistently and accurately split the tablets. But it should be realised that major saving on a few products has little effect on the overall expenditure level.

A policy of attempting to implement tablet splitting on a widespread basis as a general approach to cost cutting, however, would be likely to create problems of inappropriate drug use, with resultant toxicity, decreased compliance with therapy and less attention to patient instruction and monitoring. In many cases, the costs incurred in following this approach for some products would be greater than the saving and make the healthcare system less efficient. The combination of administrative policy-making, product evaluation, implementation of procedures and monitoring could lead to substantial administrative overhead costs that would limit savings and increase programme complexity.

Limitations to the generalisability of this study result from local costs and practices that may not be comparable to those in other countries. Local conditions may be conducive to a widespread use of tablet splitting in one area and not in another.

Conclusion

Tablet splitting has a major role in dosage adjustment in a variety of therapeutic situations. However, its potential for cost saving is limited and it is better suited to specific situations than as a method of general cost reduction in pharmaceutical programmes.

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